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IMPORTANT INFORMATION FOR WOMEN ON NEW CONTRACEPTIVES
(Particularly long-acting, hormonal implants and injectables)

Have you or other women you know been told about some marvellous new contraceptives which will keep you free from pregnancy for three months or five years?

If so, you may be about to be recruited for **clinical trials** of some **new family planning methods which have not yet been adequately tested on human beings.** Ten hospitals in different parts of the country, including **Belgaum in Karnataka and Madras in Tamil Nadu,** are already offering these new contraceptives as part of an experiment. Another 30 centres may also be distributing them soon.

Does the prospect of not constantly having to worry about getting pregnant appeal to you? Would you consider accepting one of these new, long-acting contraceptives so that you can delay or prevent pregnancy, in order to have time to recover from one pregnancy before having to cope with another one, to have some breathing space between babies, to be able to decide when to stop having children altogether, or for any other reason?

However attractive these new methods may sound, there are certain facts about them that you should be aware of before you decide whether or not to use them.

These new contraceptives come in two forms: as an injection or as an implant (six matchstick-like rods which the doctor will place under the skin of your arm through a small operation). Both contain similar substances: **artificial versions of the human hormone, progesterone.** The injection likely to be used in India soon is **Depo-Provera;** its contraceptive effect will last for three months. The implant already being tested in India is called **Norplant;** it prevents pregnancy for five years.

Many people believe that these new contraceptives are not suitable for the majority of Indian women. Here are their reasons:

1. Contraceptives like Norplant are not supposed to be used by women who have a **History of Menstrual Disorder** (irregular periods), **Anaemia** (less/weak blood), **Pelvic Inflammatory Disease** (symptom: undiagnosed white discharge), **Tuberculosis, Leprosy, Jaundice, Liver Disease, Diabetes, History of Thromboembolic Disorder** (blood clotting problems), **Heart Disease, Hypertension** (high blood pressure), **History of Allergies** (e.g. asthma, hay fever), and **Cancer.** Most Indian women suffer from one or more of these health problems at any given time. Such contraceptives are also not advised for women who are **already pregnant** or who are **breast-feeding** their babies. Considering the usual procedures followed in most family planning clinics and camps, is it likely that all these conditions will be ruled out through thorough health checkups before women are given these contraceptives?

2. These are some of the **side-effects** of hormonal contraceptives like these: **heavy and continuous bleeding and/or absence of periods, cardiac problems, liver trouble, blood clotting disorders, headache, depression, nervousness, change in appetite, nausea and weight gain.** Considering the usual state of most Indian women's health, and given their customary lack of access to healthcare services, do you think these are "minor side-effects," as some people like to claim?

3. If Norplant stays in your body for longer than five years, it can cause ectopic pregnancy (when the foetus begins to grow in the fallopian tube, instead of in the uterus). This is a dangerous situation, which can lead to the mother's death. Considering past experience with family planning staff, do you think they will be careful enough to remove the device on time? Are you sure you will remember to get it removed -- after five years?

4. No studies have clearly established that you can have babies again after using Norplant.

5. Contraceptive injections and implants can only be administered by a trained medical practitioner. With injections, you may not even know that you are being given a contraceptive. Implants can also be given to you without proper information about what it is for. Once an injection is given, it cannot be reversed until the contraceptive effect wears off. Once an implant, which is an expensive device, is placed in your body, you will have to depend on a qualified person to remove it. Considering past experience with family planning staff, are you confident that you can have it removed if and when you want -- either because of side effects or for any other reason?

6. It is said that injectable and implantable contraceptives are being offered so that women will have more choice in family planning methods and more control over their own bodies. Considering the above information as well as past experience with the family planning programme, do you think this is true?

7. Such sophisticated contraceptives require an efficient and accessible healthcare system, which will provide proper preliminary check-ups, constant follow-up and monitoring, and which will respect the patient's/consumer's wishes regarding removal of the device. Do the healthcare facilities available to you fulfil all these requirements?

As a citizen and a consumer, you have certain rights. Health or family planning workers have certain responsibilities. You have a right to full and correct information; it's their responsibility to provide this. You have a right to ask questions (about side effects, return to fertility, removal on demand, etc.); it's their duty to answer them completely and truthfully. You have a right to decide whether you want a contraceptive and to choose the one which suits your needs best;

they have no right to force or threaten you in any way to accept the contraceptive.

Before enrolling you in the trial, it's their duty to get your free, informed consent on a form which must be in a language you understand (if you cannot read, you must get a trusted person to read out to you before you sign or put your thumb impression on it). After obtaining your consent, they must conduct thorough medical tests to rule out the conditions with which you should not use such contraceptives.

Make sure that they respect your rights and fulfil their responsibilities. For more details, contact the Women's Health Team, c/o MADHYAM COMMUNICATIONS, P.B. 4610, 59, MILLER'S ROAD, BENSON TOWN, BANGALORE - 560046.

"THE PILL"

A fact file on
oral contraception

Organon

THIRTY YEARS OF ORAL CONTRACEPTIVES

A brief history of the Pill

* **1960:** Following trials in the USA, Puerto Rico and Mexico, America's Food and Drug Administration approves the Pill for use in the USA. The rest of the world follows. For example:

Argentina	1961
Australia	1961
Britain	1961
Indonesia	1961
The Netherlands	1961
Germany	1962
Brazil	1963
Denmark	1964
New Zealand	1964
Spain	1964
Italy	1965
France	1966
Norway	1966
India	1967
Greece	1968
Czechoslovakia	1972
Morocco	1973
Japan	1991 (?)

* **1967:** Following isolated and unexpected reports in British medical journals, Britain's Royal College of General Practitioners links the high dose of estrogen in the Pill to risk of thrombo-embolic disease.

* **1968:** To monitor the effect of the Pill, three prospective studies involving many thousands of women are set up: two in Britain under the control of the Royal College of General Practitioners (RCGP) and the Oxford/Family Planning Association (Oxford/FPA): and one in the USA, the Walnut Creek Study. The British studies continue today.

* **1969:** Britain's drug authority, the Committee on Safety of Medicines (CSM), recommends a top dose of 50 micrograms estrogen in the Pill. The recommendation is accepted world-wide. Enovid, the USA's first licensed Pill, contained 150 micrograms estrogen. Five years later, in 1974, a RCGP study report shows that the reduction in estrogen dose has caused a significant fall in the incidence of deep vein thrombosis.

* **1973:** The first of the "low dose" Pills appears; it contains 30 micrograms estrogen and a potent new progestogen called levonorgestrel.

* **1977:** The RCGP study finds an association between risk of cardiovascular disease and the progestogen in the Pill. Only now in the 1970s does attention shift from estrogen to progestogen. The risk is seen to be greater in women over 35, who smoke, and who have used the Pill for more than five

years. The RCGP report is a major event in the Pill's history, and at the time prompts a joint statement from the Presidents of the RCGP and Royal College of Obstetricians and Gynaecologists.

* **1978:** Bradley reports from the USA's Walnut Creek study a connection between the Pill and lipid metabolism. Later, a 1980 report from the RCGP shows that incidence of cardiovascular disease (such as heart attack and stroke) correlates with the extent to which Pills decrease levels of the protective blood lipid known as high density lipoprotein cholesterol, or HDL-C. The smaller the decrease in HDL-C, the lower the incidence of disease.

* **1981:** The first of the new generation Pills appears; it contains a new progestogen called desogestrel which appears to have minimal impact on lipid metabolism - and thus on risk factors for cardiovascular disease. This new Pill - known as Marvelon - is shown to increase levels of HDL-C. Meanwhile, a RCGP report is reassuring and instrumental in changing attitudes to the Pill. It shows virtually no risks from the Pill in the 15-35 age range - except in smokers. The report makes way for extending the age limits on Pill use to 45 for non-smokers.

* **1983:** A world Pill scare when Dr Malcolm Pike's results from California link use of the Pill to an increased risk of breast cancer. The link is later rejected.

* **1986:** Results from the Cancer and Steroid Hormone (CASH) study in the USA involving 9000 women fail to show any link between breast cancer and the Pill.

* **1987:** The CASH report confirms the results of other studies over the past decade that the Pill protects against endometrial and ovarian cancer. Risk is roughly halved, and the protection lasts after stopping the Pill.

* **1988:** London's Cavendish Clinic reports results from the world's largest-ever study of the metabolic effects of the Pill. Nine brands are examined over two years. The study, commissioned by the US government's National Institutes of Health, confirms that Marvelon does not produce the unwanted effects on lipids seen with Pills containing the progestogen levonorgestrel. Moreover, Marvelon has a positive effect on levels of HDL-C.

* **1989:** Following the published results of four studies which show a slightly raised risk of breast cancer in different sub-groups in each study, a committee of the USA's Food and Drug Administration recommends no changes in the use of the Pill or in the wording of Pill package instructions. The studies are "conflicting and inconsistent", says the expert committee.
In a later meeting at the Royal College of Medicine in the UK, Oxford FDA's principle investigator Professor Martin Vessey presents data that show that health benefits of the Pill outweigh its risks.

WHO'S USING THE PILL IN 1990?

Consumers' wider choice

The Pill picture world-wide

* According to a **Population Report** (November 1988), 63 million women throughout the world were using oral contraceptives in 1988, 24 million in developed countries, and 39 million in developing. The Pill is thus one of the world's preferred contraceptive methods. However, all users together do not exceed 10 per cent of the world's eligible population.

* In Western Europe, Australia and New Zealand, about 30 per cent of women of reproductive age use the Pill
* in North Europe (Scandinavia) 21 per cent
* in East Europe (including USSR) 6 per cent
* in South Europe 14 per cent
* in North America 18 per cent
* in China 5 per cent
* in India 2 per cent
* in Far Eastern Asia 13 per cent
* in Latin America 5 per cent

The greatest growth in use of the Pill is currently seen in developing countries where in the past decade use has risen by about 6.4 per cent per year. In 1990 the Pill remains unavailable as a contraceptive in Japan.

In other developed countries use increased by about 2.5 per cent per year during the 1980s.

The Pill picture in continental Europe

* From surveys conducted in the mid-1980s the Brussels-based International Health Foundation (IHF) found that contraceptive practice in seven European countries - Austria, Britain, France, italy, Spain, Sweden and West Germany - varied quite distinctly.

However, in five of the seven countries more than half the women surveyed had either past or present experience of the Pill. And, with the exception of Spain and Italy, the Pill was the most frequently used contraceptive method.

Among "exposed" women - that is, women aged between 15 and 44 who need contraception - the IHF found the following percentage rates of Pill use:

Austria	42 per cent
Britain	38 per cent
Sweden	37 per cent
West Germany	33 per cent
France	31 per cent
Spain	19 per cent
Italy	6 per cent

In Italy, natural or no methods (abstinence, coitus interruptus) are practised by more than half of the exposed women. Barrier methods, as in Spain, are the favoured method of birth control, relied on by 23 per cent of women.

Sterilisation, relied upon by about one quarter of Britain's couples, is very little used in France, Italy, Spain and West Germany, according to the IHF.

The IHF surveys further show that the age group most favouring the Pill is between 20 and 24 years - 72 per cent using the Pill in Britain and 56 per cent in France, for example.

* The same survey shows that women have two principal motives for using or changing their contraceptive method - reliability and effect on their health. The IHF reported: "It was astonishing to discover how many women in each country thought the Pill caused infertility or increased the risk of cardiovascular disease and cancer. These impressions appear to be entirely out of step with the facts."

Pill use in older women

* Commenting in 1986 on a 4 per cent use of the Pill among UK women aged 40 to 44, the **British Journal of Family Planning** noted: "Until recently the combined Pill was only advised for women under the age of 35; only within the last two years has this upper limit been extended for non-smoking women with no medical problems."

Thus, the current advice on Pill use and age by experts all over the world is that only women who smoke, are overweight or who have risk factors for cardiovascular disease should be advised to stop the Pill at age 35. Otherwise, healthy women can continue the Pill till at least 45.

The relaxation in age limit rules follows increasing evidence that the beneficial effects of modern low dose Pills outweigh any possible adverse effects in healthy women, whatever their age.

In particular, smoking and not age has been shown to be the single most important factor predisposing to any risk from the Pill. For example, an investigation conducted by Dr Margaret Thorogood from Oxford, UK, and presented at the 1989 world congress of the International Federation of Fertility Societies, showed that women who smoked while on the Pill were 11 times more likely to suffer a fatal heart attack than women who don't.

* Despite the reassuring news about Pill use beyond the age of 35, as many as 30 per cent of West European women of that age-group do not practise any contraception and are at risk of an unwanted pregnancy, according to the IHF's analysis. These high figures are observed in Italy and Spain; in countries recording the "safest" habits in the survey - Britain and Sweden - one in ten is at risk. Exposed older couples use the following reliable methods (%):

	Pill	Barrier	IUD	Female sterilisation	Male sterilisation
Italy					
35-39	1	19	20	0	0
40-44	0	12	4	0	0
France					
35-39	23	10	25	7	2
40-44	10	9	23	10	2
Britain					
35-39	28	15	13	13	14
40-44	3	23	7	26	28
Spain					
35-39	19	29	8	3	1
40-44	8	23	7	2	1
West Germany					
35-39	22	3	11	10	13
40-44	19	13	7	15	21
Austria					
35-39	31	15	12	2.5	7.5
40-44	21	11	8	2	5
Sweden					
35-39	20	27	31	7.5	2.5
40-44	5	35	26	10	3

The Pill was perceived as reliable by most of the older women questioned, as good for their sex life by more than half of them (86 per cent in Britain, 46 per cent in Spain) but, against current scientific evidence, as "unsafe for health" by about 80 per cent.

The IHF noted: "Heart disease and cancer were frequently mentioned in France, Great Britain and Sweden." This showed, according to the IHF, that older women have an equally or more negative opinion of the Pill than younger ones. And for these reasons, oral contraception might unjustifiably be disregarded by older couples.

REACHING NEW LEVELS OF CONFIDENCE

Health issues for the 1990s

Background

* At the end of 1989 Prof Martin Vessey and colleagues reported their latest findings in the follow-up of 17,032 women from the Oxford/FPA study in Britain. The overall relative risk* of death among the Pill user group was 0.9, so indicating that use of the Pill exerted no increased risk of death (in fact, slightly decreased the risk).

In their conclusion, the Oxford investigators said: "The results of this analysis of all 17,032 women recruited to the Oxford-Family Planning Association study give no cause for concern, in that death rate was slightly lower in the oral contraceptive entry cohort than in the diaphragm and intrauterine device entry cohort."

Cardiovascular disease

* An earlier report (May 1989) from the Oxford/FPA study suggests that risks of heart disease have been reduced by the introduction of low dose Pills. Pill users are now one third less likely to suffer a fatal heart attack than they were in the 1960s, according to Prof Vessey and his colleagues. Again, the risk to emerge from this analysis is smoking - three-quarters of the 130 women who died from a heart attack in the Oxford/FPA study were smokers.

* The Cavendish Clinic study, whose results were announced at the FIGO world congress in Rio de Janeiro in 1988, confirmed that the type of progestogen used in the Pill is crucial to its effect on the body's metabolism and thus on cardiovascular risk factors. Nearly 1500 women took part in the study, which was commissioned by the US government's National Institutes of Health, and seven different combination Pills were involved, each containing one of three progestogens - desogestrel, norethisterone, and levenorgestrel. It was by far the biggest study of its type ever undertaken.

From some 1478 measurements of blood lipids the investigators concluded that Pills containing the progestogen levonorgestrel had a strong impact on lipid metabolism and reduced levels of HDL cholesterol, the blood chemical known to protect against heart disease. Pills containing desogestrel did not produce any of these unwanted effects - indeed, Marvelon increased levels of HDL cholesterol. One of the Cavendish investigators said: "For the present time it would seem advisable to favour those formulations which have the least metabolic impact."

Thrombosis

* It was an increase in risk of thrombosis (blood clots in the veins) which caused concerns over the first high estrogen dose Pills. Subsequent studies alerted investigators that risk of thrombosis was related to the dose of estrogen, and made way for a reduction in the estrogen dose of the Pill.

The Puget Sound study in the USA followed 65,000 women from 1977 to 1982, a period in which their use of low-dose Pills increased from 16 to 39

* "relative risk" is the risk faced by an exposed population in relation to the risk faced by an unexposed control population. Numerically, it is the exposed risk divided by the control risk. A relative risk of 1 means there is no difference.

per cent. Throughout the study, the relative risk of thrombosis in Pill users fell from 8.3 to 2.9 compared with that of non-Pill users.

This trend was confirmed by the Oxford/FPA study in 1986.

Stroke

* Again, early reports in the 1960s and 1970s suggested Pill users were at an increased risk of stroke (cerebrovascular disease). The risks were particularly high in Pill users who smoked cigarettes, and the risks increased with age.

More recently, studies have not found an elevated risk of stroke in Pill users. The Puget Sound study, for example, found no increased risk from Pill use alone.

In Britain, the Oxford/FPA study in 1984 noted that there had been no cases of stroke in 9100 "woman-years" of Pill use in those women using Pills with less than 50 micrograms estrogen. However, among those using the old high-dose Pills of more than 50 micrograms estrogen, there were 13 cases of stroke in 39,400 woman-years of use.

Cancers

1. **Breast cancer.** In 1989 a reassuring conclusion was reached by the health authorities of the USA and the UK on the relation between the Pill and breast cancer. They analysed new studies published since December 1988 which showed a slight increased risk of breast cancer associated with Pill use in different **sub-groups** of women in each study.

Faced with these conflicting results, regulatory agencies like the Food and Drug Administration of the USA and Committee on the Safety of Medicines in Britain have reassured doctors and their patients that they should not alter prescribing practice or use of the Pill.

In the latest revision to the Food and Drug Administration's leaflet inserted in all American Pill packs, the FDA says: "The overwhelming evidence in the literature suggests that use of oral contraceptives is not associated with an increase in the risk of developing breast cancer, regardless of the age and parity of first use or with most of the marketed brands and doses."

In 1986 the results of the Cancer and Steroid Hormone (CASH) study were published in the **New England Journal of Medicine.** This largest case control study on the Pill and cancer risk, which involved more than 4000 women with breast cancer and 4000 controls drawn from eight American states, found no overall link between the Pill and breast cancer. Moreover, no association with early use - or with the type of progestogen - was found. The CASH study has since set the benchmark for all studies examining the relationship between the Pill and breast cancer.

2. **Ovarian cancer.** It was in 1977 that the first hint of the Pill's protective effect against ovarian cancer was made. This has now been confirmed in at least ten studies, which demonstrate a risk reduced by about 50 per cent

(ie, halved) in Pill users. Moreover, most of the studies show that the protective effect continues for several years after stopping the Pill. One study showed the risk of ovarian cancer halved after four years of Pill use, and cut by 60-80 per cent after seven or more years. The benefit was seen to last for up to 15 years after stopping the Pill.

It was suggested that as little as three months use of the Pill could offer this protection.

In a 1989 report published in the **British Journal of Obstetrics and Gynaecology**, Prof Vessey estimated that the Pill had reduced by 25% the number of deaths from ovarian cancer in women under 55 since widespread Pill use began over 20 years ago. Prof Vessey described a trend in Britain of falling deaths from ovarian cancer in young women "compatible with patterns of use of oral contraceptives."

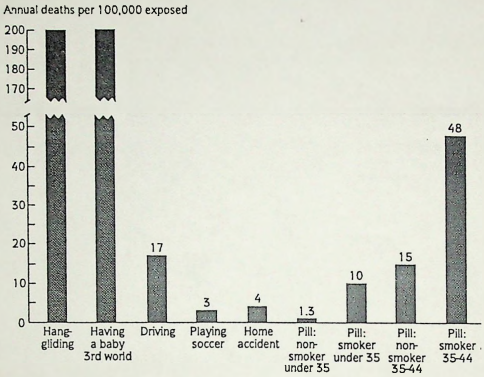
3. **Endometrial cancer.** Similarly, the Pill's protective role in endometrial cancer has now been confirmed beyond dispute. The CASH study in the USA (which also confirmed protection against ovarian cancer) found the risk reduced by about 40 per cent after two years of Pill use. Again, the protective effect increased with longer duration of Pill use, and persisted after stopping the Pill. These results have been confirmed in at least ten different studies.

4. **Cervical cancer.** Studies attempting to show an association between the Pill and cervical cancer have so far been inconclusive, not least because cancer of the cervix is now known to be caused by a sexually transmitted virus (human papilloma virus). Thus, sexual behaviour presents investigators with a statistical variable which removes much confidence from the study. The FDA's new packet insert says confidently: "A cause-and-effect relationship has not been established."

The risks in perspective

* The FDA has stressed that the risk of any form of contraception is less than the risk of pregnancy. Citing a study of Ory the FDA's packet insert says that, with the exception of Pill users who smoke, "mortality associated with all methods of birth control is low and below that associated with childbirth." Smokers on the Pill, says the FDA, have a mortality risk higher than those using other methods.

* John Guillebaud, a British family planning expert, says that women must be reminded that there are other risks in life greater than using the Pill which are all tolerated. To help physicians, he has established his own risk activity table:



Fertility after stopping the Pill

* As surveys of attitudes towards contraception show, one of the myths about the Pill is that it delays a return to fertility after stopping. The evidence does not support this view. In 1986 Professor Martin Vessey and colleagues from the Oxford/FPA cohort study of nearly 20,000 women in Britain reported that the Pill had no effect on fertility in women who had already had at least one child. "Our findings are entirely reassuring," said Professor Vessey. Nulliparous women - that's women who have not had any children - experienced a slight delay in returning to fertility, but only among older women. Professor Vessey stressed that there was no evidence at all that the Pill caused any permanent infertility.

RELIABILITY OF THE PILL

The most effective contraceptive

* Experts assess the reliability of a contraceptive by the "Pearl Index", a numerical factor expressed as the failure rate per 100 woman-years of exposure. This is calculated according to the formula:

$$\text{Pearl index} = \frac{\text{Total accidental pregnancies} \times 1200}{\text{Total months of exposure}}$$

* The Pill is consistently found to be the most reliable reversible contraceptive available. (Irreversible methods like tubal sterilisation are equally effective, but fertility cannot be simply restored.)

Indeed, surveys of attitudes to birth control suggest that the reliability of the Pill is now taken for granted and is no longer a major factor in determining choice of method - unlike attitudes of 20 years ago when reliability was a major concern in choice of method.

The table below indicates Pearl index failure rates (per 100 woman-years) of different contraceptive methods according to the Oxford/FPA study in Britain (reported in 1982 in which all women were married and over 25) and a range from other studies:

	Oxford	Others
Sterilisation		
Male	0.02	0 - 0.02
Female	0.13	0 - 0.15
Combined Pill		
High dose	0.16	0.1 - 1.0
Low dose	0.27	0.2 - 1.0
IUD		
Lippes loop	1.4	0.3 - 4.0
Modern copper	1.5	0.3 - 4.0
Diaphragm	1.9	2.0 - 15.0
Condom	3.6	2.0 - 15.0
Coitus interruptus	6.7	8.0 - 17.0
Spermicide alone	11.9	4.0 - 25.0
Contraceptive sponge		9.0 - 25.0

Gynaecologist John Guillebaud has further estimated that the likelihood of pregnancy from using no contraception during one year is about 40 per cent. This corresponds to about 10-12 live-born children in 25 years of marriage.*

* Other studies have assessed the contraceptive reliability of different Pills. For example, the aggregate Pearl index from seven studies of low dose Pills

produced the following results, and showed Marvelon (30 micrograms ethinylestradiol (EE) and 150 micrograms desogestrel) to be today's most reliable low dose Pill:

	Cycles	Pill failures	Patient failures	Pearl Index
Monophasic OCs				
Marvelon	23,258	0	1	0.05
Norethisterone/EE	16,345	0	3	0.22
Gestodene/EE	36,771	2	5	0.23
Levonorgestrel/EE	11,064	1	2	0.33
Norgestimate/EE			16	0.86
Triphasic OCs				
Norethisterone/EE	14,222	2	?	0.17*
Levonorgestrel/EE	35,036	2	7	0.31

* Pill failures only

HOW CAN THE PILL BE GOOD FOR YOU?

The non-contraceptive benefits

* In developing countries especially, regular use of a reliable contraceptive has enormous benefits on the quality of maternal and child health. Indeed, the benefits are such that in many developing countries the very future of their economy depends on wide and continued use of reliable contraception.

According to a **Population Report** (November 1988), an estimated half million women die in pregnancy and child birth each year. Almost all these deaths occur in developing countries, where - with the exception of China - on average 550 women die for every 100,000 live births (or one for every 180 live births). As many as one in five babies die in parts of Africa and Asia.

It is now agreed that pregnancies are high risk because they occur too soon (before the age of 18), too late (after 35), are too many (more than four), or too close together (less than two years apart). Avoiding these high risk pregnancies would prevent two in every five maternal deaths and some six million infant deaths per year.

* The Pill is not only the most reliable reversible contraceptive; the USA's cautious Food and Drug Administration has for the first time ever now included non-contraceptive health benefits on its detailed Pill packet inserts. The FDA groups the benefits into three categories: effects on menstruation; effects related to inhibition of ovulation; and effects from long-term use.

Menstrual benefits

1. **Better cycle regularity.** The effect of the Pill on cycle regularity is to produce a regular four-week cycle and reduce prolonged and excessive bleeding. One consequence of the last effect is that women on the Pill are less likely to suffer iron-deficiency anemia (at menstruation Pill users lose only half the body's blood iron which non-Pill users lose). A 1974 report of the RCGP showed that Pill users had 45 per cent less iron-deficiency anemia than non-users. This finding is especially important in countries where nutrition is poor.

In an Italian study of Marvelon reported in 1988 a regular cycle was experienced by 95 per cent of 11,605 users by the sixth cycle of use. The proportion of women experiencing prolonged bleeding fell from 8 to 0.6 per cent, and excessive bleeding from 21 to 3 per cent.

2. **Less dysmenorrhea.** Studies show that about one half of all women suffer pelvic pain during menstruation. The RCGP study showed that dysmenorrhea was 63 per cent less common among Pill users than among non-Pill users. In fact, the Pill is usually prescribed by doctors as a treatment for women (about one in ten) whose dysmenorrhea interferes with their everyday lives.

Benefits from inhibited ovulation

1. **Reduction in ectopic pregnancy.** Ectopic pregnancy, which occurs when the embryo develops outside the uterus, is a life-threatening disorder requiring major surgery.

2. **Reduction in functional ovarian cysts.** This finding was first reported in 1974 and has since been confirmed in other studies. A reduction in cysts is thought to occur because the Pill suppresses the cyclical activity of the ovary.

Benefits from long-term use

1. **Less benign breast disease (fibroadenoma and fibrocystic disease).** It is estimated that between half and three-quarters of all benign breast disease which would occur in Pill users is prevented because of the Pill. It is thought that in the USA the Pill prevented more than 23,000 surgical procedures for benign breast disease in the 1970s. The Oxford/FPA study suggested that the progestogen in the Pill could be the reason.
2. **Less pelvic inflammatory disease.** Women who use the Pill appear to halve their risk of developing pelvic inflammatory disease (PID). This finding emerged after 11 studies had been analysed in the early 1980s. This is an important finding in itself, but especially important as PID - an infection which begins in the cervix and climbs to the upper reproductive tract - is a major cause of blockage in the fallopian tube, and hence of infertility. At the 1989 world congress of the IFFS, WHO experts spoke of a world epidemic of infertility as a result of PID. PID is also a major cause of ectopic pregnancies. An American analysis indicated that 600 of every 100,000 Pill users would be prevented from suffering a first episode of PID because of the Pill.
3. **Reduced endometrial and ovarian cancer.** The protection given by the Pill against both these cancers has now been proved beyond dispute. The risks are approximately halved, and are prolonged beyond stopping the Pill.

* Howard Ory, of the Centres for Disease Control, Atlanta, USA, has written: "The magnitude of these preventive effects, particularly against pelvic inflammatory disease and benign breast disease is substantial... In addition, by limiting oral contraceptive use to younger women who do not smoke, one can tilt the balance toward the protective effect by largely eliminating the risk of cardiovascular disease."

Thus, the Pill becomes of positive health benefit - and can be good for you!

Further advantages described by Pill users

1. **Postponing withdrawal bleeds.** Who wants her period on holiday; or on her honeymoon; or during exams; or during the season's top games final? Because the menstrual cycle of women on the Pill is controlled by the Pill itself, postponing a bleed for a few days or even weeks presents no problems, by simply skipping the seven tablet-free days between packets. The procedure is much simpler for "monophasic" single-dose Pills than for phasic Pills.

2. **Cosmetic benefits.** Hormones, and particularly those known as androgens, are partly responsible for acne and unwanted hair (hirsutism). In the past, older Pills contained hormones (like levonorgestrel) which are rather androgenic, so girls could find their acne worsening when they went on the Pill. Modern Pills contain progestogens like desogestrel which are not androgenic, and thus have no adverse effect on acne. Indeed, studies on Marvelon have shown that the numbers of spots can even be reduced. One

study described at the world obstetrics and gynaecology congress in Rio de Janeiro in 1988 showed that average numbers of facial spots were reduced from 15 to 6 after six cycles use of Marvelon. This was an improvement comparable with specific anti-acne therapies. Another study from Italy found that of 1021 women with acne it disappeared in 754 after six months on Marvelon.

HOW THE PILL WORKS

Preventing ovulation

The normal menstrual cycle

* The human female's store of eggs lies in the ovaries. One egg is released once a month when chemical messengers from the pituitary gland in the brain stimulate development of some eggs and the release of one of them. The release is known as ovulation, and takes place roughly midway in the menstrual cycle.

The messenger which stimulates the development of an egg is a hormone, called follicle stimulating hormone (FSH). However, two other important hormones are at work during the cycle which act together to prepare the womb and body cells for pregnancy. They are called estrogen and progesterone.

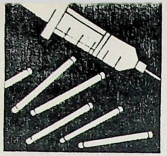
However, pregnancy only occurs when an egg released from the ovaries is fertilised by a sperm swimming along the fallopian tubes to meet it. Just one sperm is enough to complete the fertilisation. The fertilised egg (embryo) embeds in the wall of the womb. Once the embryo has implanted in the womb, pregnancy has begun. Levels of estrogen and progesterone continue to rise throughout pregnancy, and the production of eggs in the ovaries stops.

The oral contraceptive

* The Pill works by mimicking this hormone production seen in pregnancy. For most of today's Pills contain a combination of these two hormones active during pregnancy - estrogen and progestogen. So a raised level of these hormones in the blood stops the messages of the pituitary gland by blocking FSH production, so preventing the development of eggs. In this way, ovulation is prevented, so no fertilisation can take place.

* The hormones used in the Pill are man-made, but throughout the Pill's 30 year history efforts have been made to produce compounds which act as closely to nature as possible. The latest generation of progestogens, like desogestrel is very close to natural progesterone and - according to many experts - unlikely to be improved upon in the foreseeable future. (Which is why in the West - despite interest in such new contraceptive methods as vaginal rings, transdermal implants or male vaccines - the Pill is likely to remain the favoured and most successful method of birth control.)

* In most cases a Pill is taken for 21 consecutive days. This period is followed by seven Pill-free days during which levels of estrogen and progestogen in the blood go down. As a result, the mucous lining of the womb - which has apparently been preparing to receive an embryo - is shed, and a monthly bleeding occurs just as in normal menstruation.



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INJECTABLES AND IMPLANTS

Population Information Program, The Johns Hopkins University, Hampton House, 624 North Broadway, Baltimore, Maryland 21205, USA

Hormonal Contraception: New Long-Acting Methods

Editors' Summary. Before the year 2000 women around the world may have up to five new family planning methods to choose from. All will be very effective, convenient to use, and long-acting—from one month to five years. All use a progestin, a type of female hormone that is also used in birth control pills. One new method, Norplant, has already been approved in seven countries. Other new methods are in various stages of development and testing. The new methods share one obvious disadvantage. To varying degrees, all change or disrupt menstrual patterns. If women expect this and know it is not harmful, many are willing to accept it.

Norplant implants have been approved in Finland, Sweden, Ecuador, the Dominican Republic, Indonesia, Thailand, and Colombia, and applications are pending elsewhere. Already about 75,000 Indonesian women have used Norplant. Placed just under the skin on the inside of a woman's arm, six capsules release the progestin levonorgestrel at a slow, steady rate. For five years they prevent nearly all pregnancies. Then they must be replaced. Similar products, using different progestins and/or fewer implants, are being developed. Norplant-2, a 2-rod system that lasts at least three years, has been approved in Finland. Application for US approval will be filed in 1987.

Biodegradable implants also are placed under the skin, but they eventually dissolve and disappear. There are two types—(1) Capronor, a single capsule containing levonorgestrel, and (2) three or four pellets of the hormone norethindrone combined with small amounts of cholesterol. Capronor is expected to prevent pregnancy for at least 18 months; the pellets, for at least 12 months. They may be available by the mid-1990s.

Injectable microspheres and microcapsules, suspended in a solution, are given with a hypodermic needle. The tiny particles of different sizes, consisting of hormone in a polymer carrier, dissolve and release hormone at various rates, providing a nearly constant dose that prevents pregnancy for one to six months. The first microsphere contraceptive may be available in some countries in the early 1990s.

Monthly injectables add an estrogen to a progestin to minimize menstrual changes. Some 1.5 million women in China and Latin America already use monthly injectables. Two new monthly injectables may be available as early as 1988.

The **vaginal ring** is placed by the woman in her vagina, where it gradually releases hormone. A 3-month levonorgestrel ring may be available in some countries by 1988. A 3-month progesterone ring is being developed for breast-feeding women.

The precursors of these new methods are the **long-acting injectable contraceptives**—the 3-month Depo-Provera and the 2–3 month Noristerat. They have been available for over a decade. Depo-Provera is approved for contraception in at least 90 countries; Noristerat, in more than 40. Some five million women use them. Animal studies raised fears that long-acting injectables might cause cancer. Preliminary results from new studies of women are reassuring for the most part, but some questions remain.

When new long-acting methods become available, marketing and program development are essential. Production must be arranged; providers trained; logistics systems in place; and supplies available. The media, the health care professions, and other opinion leaders must be thoroughly briefed in advance. Couples must learn about the new methods. If these are properly introduced and made continuously available, there will soon be a much broader choice of contraceptives for women. Effective, reversible, long-acting hormonal contraception will be available for nearly every couple, whatever their plans and needs. **End of Editors' Summary.**

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NORPLANT IMPLANTS

Norplant* implants consist of flexible, nonbiodegradable tubes filled with levonorgestrel, a synthetic hormone of the progestin family. The implants are placed under the skin on the inside of a woman's upper or lower arm. The hormone is slowly released at an almost constant rate for several years. Developed by the Population Council, Norplant has been tested in more than 44,000 women in 31 countries (189). It has proved to be highly effective, safe, and well-liked by its users. By 1987, a 6-capsule Norplant system had been approved for marketing in seven countries—Finland, Sweden, Indonesia, Thailand, Ecuador, the Dominican Republic, and Colombia (85). Applications for approval have been filed in many other countries.

Norplant implants come in two forms. The first, called simply Norplant, consists of six hollow Silastic (silicone rubber) capsules. Each capsule is 34 mm long, with a diameter of 2.4 mm, and contains 36 mg levonorgestrel. The ends of the capsules are sealed shut with Silastic adhesive. This is currently the more widely used of the two systems. It is highly effective in preventing pregnancy for five years. The newer system, called Norplant-2, consists of two solid Silastic rods, each 44 mm long. A total of 70 mg levonorgestrel is dispersed in the matrix of each rod. Norplant-2 is highly effective for at least three years. This system was approved in Finland in 1987. An application for approval in the US will be filed in 1987. The materials in Norplant and Norplant-2—Silastic rubber, Silastic adhesive, and levonorgestrel—have been used safely for years in a variety of medical applications (192). Levonorgestrel is the progestin in several popular brands of oral contraceptives.

Preintroductory trials of Norplant have taken place all over the world. Over 40 percent of participants are in Asia and the Pacific, primarily in China, Indonesia, and Thailand. Another 30 percent are in Latin America, primarily in Brazil, the Dominican Republic, and Ecuador. About 2,500 Egyptian women and more than 1,000 women in sub-Saharan Africa also have participated. Preintroductory trials of Norplant-2, involving more than 4,500 women, are in progress in Chile, Colombia, China, the Dominican Republic, Ecuador, India, Mexico, Thailand, and the US (192).

With both Norplant and Norplant-2, levonorgestrel diffuses through the Silastic membrane at a steady, slow rate. Within 24 hours after insertion, levels of levonorgestrel in blood plasma are high enough to prevent ovulation (18). The daily release averages 50 to 80 µgs in the first year of use, then declines to about 30 to 35 µgs per day over the next five years (18, 56, 208). In the first year, this is about the same as the daily dose of levonorgestrel in progestin-only oral contraceptives and one-fourth to one-half the dose in combined estrogen-progestin oral contraceptives.

Insertion and Removal

Inserting and removing Norplant implants are usually minor surgical procedures that require local anesthetic and a small incision (see box, p. K-62). Removal is more difficult and takes longer than insertion. If health workers are adequately trained and maintain sterile conditions, however, complications are unlikely to occur with either procedure.

The best time to insert Norplant implants is when a woman is menstruating or no later than five to seven days from the start of menstrual bleeding. This ensures that she is not pregnant. At other times, the woman should be given another contraceptive method for the rest of her cycle and asked to return to the clinic when she is menstruating (180).

Norplant capsules and rods are inserted just under the skin usually in the inside of the upper or lower arm. An experienced practitioner can insert the six capsules in 5 to 10 minutes. The two rods in Norplant-2 are easier to insert and remove than the six capsules in Norplant (6, 115, 191).

In multicenter clinical trials infection and other complications after insertion have been rare; only 3 women in every 1,000 ever developed infections (235). In an Indonesian study, however, there were 12 infections treated with antibiotics in 828 insertions, or 14 per 1,000 (6). With the exception of one trial in India (115), studies show that the capsules or rods are rarely expelled. Expulsion may occur if the insertion site becomes infected (269) or if the im-

* NORPLANT is the registered trademark of the Population Council for contraceptive subdermal implants.

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plants are placed too close to the incision (232). Bruising often occurs during insertion. Rare complications are mild itching and formation of scar tissue around the incision (147, 269).

Insertion causes little or no immediate pain for most women, although the area may be bruised and sore for several days. Among 700 Thai women, for example, 69 percent reported feeling no pain during insertion, 28 percent felt slight discomfort, and only 3 percent reported moderate to severe discomfort (211). The capsules and rods are flexible and fairly soft. Once inserted, they do not cause any pain or interfere with a woman's activities (191).

Removing 6-capsule Norplant usually takes about 15 to 20 minutes and usually requires only one small incision. In one US trial about 20 percent of 106 removals took more than 30 minutes, however. Ordinarily, only one incision was needed, but in about 5 percent a second incision was needed. As the nurse-practitioner performing removals became more experienced, however, problems were much less frequent (52). Generally, implants are relatively easy to remove if they were inserted properly—that is, just under the skin. They are harder to remove if they were inserted deeply (6, 132). Sometimes one or more implants, or a piece of an implant, cannot be removed easily. Occasionally, the implants cannot be removed on the first attempt. How often these problems occur has not yet been determined.

When the implants are removed, a new set can be inserted immediately. If the original implants have been removed easily and the insertion site is not swollen, the new implants can be inserted in exactly the same place. If the removal causes swelling or trauma, however, the implants should be inserted either in the other arm or through the original incision but facing the opposite direction (191).

How often do complications occur after removal of the implants? In two US trials no infection or other complications have occurred after a total of about 150 removals (52, 132). In 122 removals at an Indonesian clinic, 11 hematomas (bleeding under the skin) and two infections occurred in the week after removal (6). No treatment was needed for the hematomas. The infections were treated with antibiotics (275). Information is not available from other countries. As implants become more widely available and as less experienced doctors perform insertions

An Indonesian woman tells a friend about Norplant in this drawing from a pamphlet prepared for the Indonesian National Family Planning Coordinating Board (BKKBN) by PATH/PIACT.

Table 1. Characteristics and Status of Nonbiodegradable Implants as of March 1987

Delivery System	Development & Testing	Hormone	Duration of Action	Status of Animal Trials	Status of Human Trials			Estimated Availability
					Phase I	Phase II	Phase III	
Norplant (6 capsules)	Population Council	Levonorgestrel	5 years	Completed	Completed	Completed	Completed or underway in 31 countries in over 44,000 women[1]	Approved in Colombia, Dominican Republic, Ecuador, Finland, Indonesia, Sweden & Thailand. Widespread availability by early 1990s.
Norplant-2 (2 rods)	Population Council	Levonorgestrel	At least 3 years	Completed	Completed	Completed	Underway in 9 countries in 4,500 women	Approved in Finland. More approvals in late 1980s.
1 rod[2]	Population Council	ST-1435	2 years	Partially completed[3]	Completed	Completed[4]	Planned	Mid-1990s
1 rod[2]	Population Council, Organon International	3-keto desogestrel	2½–4 years	Completed	Completed	Underway in 3 countries	Planned	Early 1990s

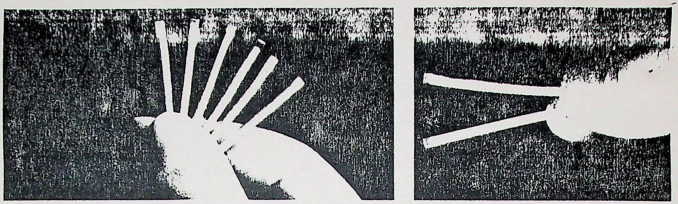
Note: Phase I trials are conducted in small numbers of volunteers to determine how a drug is absorbed, metabolized, and excreted from the body and to determine tentatively delivery method and safe dosage. Phase II trials usually involve 20 to 50 volunteers for three months to assess safety and efficacy and to evaluate delivery method further. Phase III trials involve at least several hundred volunteers—and often thousands—for two years or more to confirm safety and efficacy.

[1]Some of these trials were not intended to meet requirements for regulatory approval.

[2]Trade name not yet chosen

[3]Trials ongoing in some animal species

[4]Phase II trials being repeated with modified delivery system



Population Council

Norplant implants release the progestin levonorgestrel. They are inserted just under the skin in the arm. The 6-capsule system (left) provides almost complete protection from pregnancy for five years. Norplant-2 (right), using two rods, is effective for at least three years.

and removals, training programs must emphasize the importance of sterile technique to prevent infection.

There are few contraindications to Norplant use. The implants are not recommended for women using medication to prevent blood clots or for women with active liver disease, jaundice, undiagnosed abnormal genital bleeding, or bleeding disorders (269). Norplant also is not currently recommended for breast-feeding women because few studies have looked at potential risks to nursing infants (191).

Effectiveness

Norplant provides almost complete protection against pregnancy. In the first five years of use of the Norplant 6-capsule system, the chances of pregnancy are less than one per 100 women per year (see table 2). This rate is lower than for oral contraceptives, intrauterine devices, and barrier methods. Effectiveness decreases slightly after five years, and in the sixth year 2.5 to 3 percent of users conceive (18). Thus replacement after five years is recommended. A slight and gradual decrease in the daily release of levonorgestrel over time probably accounts for the increase in pregnancies after five years (168).

Ongoing international trials show that Norplant-2, the 2-rod system, is as effective as the 6-capsule system for the first three years of use (19, 115). It was expected that Norplant-2, like Norplant, would be effective for five years. After three years, however, an unexpectedly high number of pregnancies occurred in a large 5-country trial. The cumulative failure rates ranged between 5 and 6 percent at the various centers. As a result, the Population Council has asked clinical investigators in this study to remove Norplant-2 after three years (232). Other studies have reported few pregnancies so far, and most are continuing into the fourth year (232).

It is not yet clear why the pregnancy rate with Norplant-2 increased in the 5-country trial. Presumably, the release rate of progestin declined. The Population Council is conducting extensive laboratory tests to find the reasons for this.

Precisely how Norplant prevents pregnancy is not fully understood. Like other progestin-only contraceptives, Norplant implants appear to prevent pregnancy in several ways. Norplant suppresses ovulation in at least half of menstrual cycles (18). Hormonal indicators of ovarian activity suggest that ovulation may occur in some of the remaining cycles (49). Even if ovulation does occur, levonorgestrel makes cervical mucus thick and scanty, and sperm cannot easily pass through it into the uterus to fertilize ova (18, 269). Levonorgestrel also suppresses the

Advantages and Disadvantages of Norplant Implants

Advantages

- Norplant is highly effective.
- Once in place, the implants require no further action until removal.
- The 6-capsule system provides continuous protection for five years.
- The implants have no estrogen and thus no estrogen side effects.
- The contraceptive effect of the implants ends soon after they are removed.
- The implants release progestin at a fairly constant, low rate, avoiding the high initial dose typical of injectables and the daily surge of hormones with oral contraceptives.
- Norplant may help to prevent anemia.

Disadvantages

- Norplant must be inserted and removed by health professionals.
- Health workers need special training and practice to insert and remove implants.
- Norplant implants are initially more expensive than oral contraceptives and other short-term methods.
- Norplant often changes bleeding patterns.
- Women cannot discontinue use on their own.
- Some women may be reluctant to use an unfamiliar method.
- Implants may be visible.

Table 2. Performance of Norplant Implants, Selected Trials, Including Comparisons with IUDs, 1982–1986

Length of Follow-Up, Author, Date (Ref. No.)	Place	Device	No. of Women	Cumulative Net Termination Rates per 100 Women for: Pregnancy	Menstrual Problems	Infection	Other Medical	Expulsion	Non-medical	Continuation Rate
12 Months										
Lopez et al. 1986 (154)	Colombia	Norplant	389	0	6	<0.5	2	0.5	1	92
Lubis et al. 1983 (155)	Indonesia	Norplant	813	1	2	<0.5	1	NA	1	95
Marangoni et al. 1983 (158)	Ecuador	Norplant	283	0	7[a]	1	3	0	1	87
		TCu 200	283	2	2[a,b]	1	1	3	2	88
Satayapan 1983 (211)	Thailand	Norplant	704	<0.5	4	2	5	NA	2	88
Shaaban et al. 1983 (221)[c]	Egypt	Norplant	250	1[d]	7[b]	0	1	0	2	90
		TCu 380A	100	1	6[b]	0	1	2	3	87
24 Months										
Affandi et al. 1984 (5)	Indonesia	Norplant	451	<0.5	4	<0.5	2	NA	2	92
Indian Council of Medical Research 1986 (115)[e]	India	Norplant	88	0	15	NA	NA	4	6[g]	77
		Norplant-2	84	0	20	NA	NA	6[f]	12[g]	66
Lopez et al. 1986 (154)	Colombia	Norplant	389	0	14	<0.5	<0.5	0	3	77
Shaaban & Salah 1984 (217)	Egypt	Norplant	250	1[d]	16	0	5	0	9	68
		TCu 380A	100	2	21[b]	0	9	3	13	52
36 Months										
Bardin et al. 1986 (19)	NA	Norplant	300	2	16	NA	11	NA	10	61
		Norplant-2	750	1	16	NA	10	NA	12	61
60 Months										
Affandi et al. 1987 (7)	Indonesia	Norplant	[illegible]	2	9	NA	4	0	7	78
Diaz et al. 1982 (56)	Chile	Norplant	101	0	10	NA	14	NA	22	54
Shaaban 1987 (216)	Egypt	Norplant	250	2	19	NA	7	0	14	58
Sivin 1984 (228)	Finland, Chile, Dominican Republic	Norplant	324	1	14	<0.5	14	NA	29	42

Note: Rates may not add to 100 due to rounding.
[a]Difference statistically significant
[b]Includes pelvic pain
[c]Rates calculated for nine months of use
[d]All pregnancies probably conceived before Norplant use
[e]Gross termination rates
[f]Local inflammation reported in 2 of 4 cases of expulsion
[g]Includes some medical

cyclic development of the endometrium in over 50 percent of Norplant users (51).

Menstrual Changes

Irregular menstrual bleeding is the most common side effect of Norplant. About 60 percent of women notice changes in their menstrual patterns in the first year after Norplant insertion (211, 233, 269). Most common are an increase in the number of days of bleeding and/or spotting per cycle and a decrease in the length of the menstrual cycle. For many women irregular bleeding decreases over time, however. Among the women who used the 6-capsule system for five years, the average number of days of bleeding and spotting per year gradually dropped from 92 in the first year of use (an average of seven days per cycle) to 70 in the fifth year (five per cycle) (19). Amenorrhea (absence of menstrual bleeding) is less common than prolonged bleeding or spotting, but in one multicenter study 25 percent of users did not menstruate for at least 90 days during the first year of use (233).

These menstrual changes have no apparent harmful effects. Although many women bleed more often than before, the volume of blood lost does not change (169). Heavy bleeding is quite rare (269). In fact, in four studies average hemoglobin levels increased significantly after Norplant insertion—a change that may help prevent anemia (94, 139, 221, 233). In three other studies average levels remained the same (155, 169, 210).

Reproductive Effects

No serious reproductive side effects have been reported among Norplant users. Transient ovarian cysts have been found in as many as 10 percent of users (56, 139). Some of these cysts have grown to 10 cm. Surgery to remove the cysts, removal of the implants, or other treatment is usu-

Implants should be gently inserted just beneath the surface of the skin. Inserting them too deeply makes removal difficult. (Courtesy of Kee Kee Minor, AVSC)

Inserting and Removing Norplant Implants

Inserting Norplant implants is a simple procedure. Removal is more difficult. With careful training and the supervision of an experienced practitioner, however, doctors, nurses, and other health workers can perform both procedures.

Insertion

Implants are inserted on the inside of the upper or lower arm 6 to 8 cm above or below the elbow. Inserted through a single incision, the six Norplant capsules form a fan shape, with its base toward the incision. Special care must be taken during insertion to place the implants just under the skin. If the implants are inserted too deeply, locating and removing them can be difficult. Maintaining sterile technique throughout the procedure is essential to prevent infection.

For the most part, only basic surgical equipment is needed: a table for the woman to lie on and a support for her arm, sterilized surgical cloths, sterile gloves without talc, soap, an antiseptic solution such as betadine, local anesthetic, a 4 to 4.5 cm anesthetic needle and syringe, scalpel, tweezers or mosquito forceps, butterfly skin closures, and sterile gauze and compresses. In addition, a specially marked #10 trocar is needed.

To insert Norplant implants:

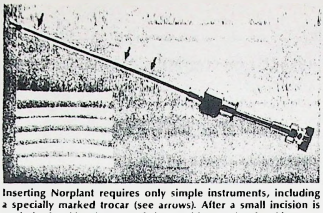
1. Wash the insertion area, apply antiseptic solution, and, if possible, cover the area below the arm with a sterile cloth.
2. Anesthetize the insertion area with local anesthetic, such as lidocaine 1%: inject a small amount into the incision area, then turn the needle and anesthesize the six or two areas, 4 to 4.5 cm long, where the implants will be inserted. Apply the anesthetic just beneath the skin. This raises the outer layer of skin from underlying tissue and makes insertion easier.
3. With the scalpel or the trocar, make a 2 mm incision parallel to the bend in the elbow.
4. Insert the tip of the trocar through the incision. The trocar is marked in two places—near the top and near the tip (see photo, p. K-63). Gently advance the trocar into the incision to the mark near the top of the trocar—about 4 to 4.5 cm. While advancing the trocar, keep upward pressure on it without changing the angle of insertion so that the implants will be inserted just below the skin.
5. Load the implant into the trocar. With the plunger, gently push the implant towards the tip of the trocar until you feel resistance. Then bring the trocar back, keeping the plunger stationary, until the mark close to the tip is visible in the incision and you feel the implant pop out of the trocar. Leave about 0.5 cm between the incision and the tips of the implants. Do not remove the trocar from the incision. Feel the arm to make sure the implant is in place.
6. Load the second implant into the trocar. To place the next implant, change the direction of the trocar so that the next implant will be angled 15 degrees from the first implant. Place your finger on top of the first implant. Advance the trocar alongside your finger to the mark near the top. Then release the implant under the skin by pulling back the trocar. Repeat the procedure until all implants are inserted.
7. After all the implants are inserted, apply pressure to the incision with sterile gauze to minimize bruising and to stop bleeding. Then press the edges of the incision together and close it with a butterfly closure. Sutures are not needed.
8. Cover the incision with a dry compress and wrap gauze around the arm to prevent bleeding. Tell the woman to keep the bandage clean and dry for four days (132, 144, 182, 191).

Removal

Removing the implants is usually more difficult than inserting them. Problems can occur if insertion was done improperly—that is, if the implant was placed too deep in the tissue—or when fibrous tissue has grown around the implants, as often happens. Practitioners should work gently, carefully, and patiently to avoid injuring the skin of the arm. Along with equipment used for insertion, mosquito and Crile forceps are needed for removal.

To remove the implants:

1. Wash the woman's arm and apply antiseptic. As during insertion, sterile technique is essential.
2. Locate the implants with your fingers. The locations of the implants can be marked with a pen.
3. Apply a small amount of local anesthetic *under* the ball of the implants nearer the elbow. Applying anesthetic over the implants makes the skin swell and blocks your view of the implants.
4. Make one 4 mm incision as close as possible to the ends of all the implants, at the base of the "fan." This incision is long enough to remove all implants. A longer incision does not make removal easier.
5. Remove first the implant that is closest to the incision or closest to the surface.
6. Gently push the implant toward the incision until the tip is visible. Grasp the tip with the mosquito forceps. Scrape away the fibrous tissue around the implant with gauze or, if necessary, cut with a scalpel. If you use a scalpel, be careful not to cut the end of the implant. Grasp the implant with the Crile forceps and remove it.
7. If you cannot push the implant into the incision, insert closed forceps into the incision and gently dissect the tissues around the implant. At the same time push the implant toward the incision with your other hand.
8. Apply more anesthetic as needed to remove the other implants.
9. If the woman does not want a new set of implants, close and bandage the incision as you would after insertion. If she does want a new set, it can be inserted immediately (see p. K-59).
10. If an implant cannot be removed, the woman should return to the clinic in about two to four weeks. Removing the remaining implant or implants is easier when the arm has healed (6, 144, 182, 191). Of course, the woman should receive another contraceptive method to prevent pregnancy until she returns.



Inserting Norplant requires only simple instruments, including a specially marked trocar (see arrows). After a small incision is made in the skin, the trocar is inserted just under the skin up to one of the marks away from the tip—the middle mark for Norplant, the upper mark for the longer Norplant-2. Then the plunger is held in place and the sleeve withdrawn until the mark near the tip shows and the implant pops out of the trocar. Sterile technique is essential throughout the insertion procedure.

ally not needed, however, since the cysts regress spontaneously within six weeks (18, 19).

Concerns have been raised about an increased risk of ectopic pregnancy among Norplant users. These concerns are because higher than expected rates of ectopic pregnancy have been reported among women using progestin-only oral contraceptives (30, 32, 152, 238). As of January 1987, in studies of Norplant and Norplant-2 conducted by the International Committee for Contraception Research, 10 ectopic pregnancies had been reported in 6,800 woman-years of use, for a rate of 1.5 per 1,000 woman-years (232). This is about the same as the rate among women using copper and unmedicated intrauterine devices (IUDs), excluding the Dalkon Shield, and probably does not represent an increased risk for Norplant users. The rate is lower than the rate among women using no contraception (231, 256). Certainly, any pregnancy during Norplant use is rare.

The contraceptive effect of Norplant wears off quickly once the implants are removed. Former users of Norplant conceive as rapidly as women who have not used contraception. Among 99 women seeking to become pregnant, 50 percent conceived by three months after discontinuation, and 86 percent, by one year (232).

Preliminary evidence suggests that the small amount of levonorgestrel released by Norplant has no harmful effects on infants exposed during pregnancy or breast-feeding. To date, researchers have followed up 15 full-term pregnancies conceived during Norplant use. All pregnancies were normal, and the children, healthy (232). This number would be too small to detect most birth defects, of course, and follow-up is too short to detect any possible long-term effects.

In Chile and Indonesia researchers have compared breast-feeding infants of mothers who used Norplant with infants of mothers who used copper-T IUDS. In Chile there was no difference between the two groups in the percentages receiving supplementary bottle-feeding in the first six months postpartum, in the percentages still breast-feeding at 12 months, or in average monthly weight gain. Infant daughters of Norplant users gained less weight than daughters of IUD users, but weight gain for all children was within the normal range (55). The study is continuing; researchers will look for any long-term effects (232). In Indonesia both groups of infants grew satisfactorily in weight and length over six months. In fact, the Norplant infants gained weight slightly but significantly faster (4).

Norplant use during breast-feeding does not alter hormone levels in infants. Serum levels of immunoglobulins and urinary levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), and testosterone are the same in breast-fed infants of women using Norplant and of women using barrier methods or no contraception (1, 114).

Other Side Effects

Norplant causes few side effects apart from menstrual changes. Headache is the most common other complaint (154, 221, 229, 235). In one study Norplant users reported more headaches than IUD users (229). In another, however, rates were the same (221).

Norplant causes few systemic changes. Lipid metabolism is especially important because of its link with cardiovascular disease. Six studies to date have reported conflicting results (50, 94, 105, 210, 218, 279). Other clinical indicators are reassuring. Only minor changes—all within the normal range—have been observed in liver function (48, 50, 94, 210, 220), carbohydrate metabolism (50, 94, 269), blood coagulation (219), blood pressure (139, 155, 210, 220), immunoglobulins (1, 269), serum cortisol (21), urea nitrogen, uric acid, sodium, potassium, calcium, inorganic phosphorous (48, 50, 269), and body weight (139, 155, 221, 235).

Care of Equipment for Norplant Insertion and Removal

Special care should be taken with the equipment used during Norplant insertion and removal. The trocar should be washed with warm water and antiseptic solution immediately after each insertion and then disinfected before reuse. The equipment can be disinfected by several methods:

- autoclave for 20 minutes,
- immerse in boiling water for 5 to 10 minutes, or
- cold-sterilize with standard hospital-strength germicide for at least one hour.

Autoclaving is the most effective disinfection method. All three methods will kill human immunodeficiency virus (HIV), the virus that causes AIDS (68). Neither cold sterilization nor boiling in water for 5 to 10 minutes kills hepatitis B virus, however. Where hepatitis is endemic, instruments should be autoclaved or boiled in water for 15 to 30 minutes.

The tip of the trocar becomes blunt after repeated use, and this makes it harder to advance the trocar into the incision. Health workers should examine the tip of the trocar after every 10 insertions and sharpen it as needed (188). With proper care a trocar can be used for about 50 insertions (124). If incisions are made with the trocar, it may need sharpening more often and may not be usable for 50 insertions.

Continuation

Over two thirds of women use Norplant implants for at least two years. After one year, continuation rates range from 87 to 95 percent, and after two years, from 66 to 92 percent (see Table 2). In a multicenter Indonesian field study involving more than 8,600 women after 12 months 95 percent of the urban participants and 98 percent of the rural participants were still using Norplant; at 18 months, 92 and 98 percent (277). According to smaller studies in Chile, the Dominican Republic, Egypt, Finland, and Indonesia, after five years 42 to 78 percent of users were still relying on implants (56, 228). Bleeding irregularity is the most frequent reason for discontinuation, causing 2 to 7 percent of women to stop using implants in the first year (see Table 2). This is lower than discontinuation rates for bleeding problems with long-acting injectables (see p. K-72). The greater difficulty of discontinuing Norplant may help account for the difference in discontinuation rates.

The long effectiveness and ease of use of Norplant are among its most attractive features. In Thailand, for example, 31 percent of 700 women reported that five years of effectiveness was the major reason that they chose Norplant over other methods (211). Focus-group discussions among Norplant users in the Dominican Republic, Ecuador, Indonesia, Kenya, the Philippines, Sri Lanka, and Thailand identified other desirable features of the method as well: not having to put anything into the vagina, not having to do anything just before intercourse, reversibility, and the possibility of slight weight gain (a much less common side effect than menstrual irregularity), which most women considered a sign of good health (184, 274).

Use of Norplant

Data on use of the 6-capsule Norplant system are available for only four of the seven countries where it has been approved; the other three countries have granted approval only recently. In Indonesia Norplant is available through the Indonesian family planning program at more than 150 locations, mostly in Java. The Indonesian National Family Planning Coordinating Board (BKKBN) buys Norplant directly from the manufacturer using grant funds from the United Nations Fund for Population Activities (UNFPA) and loan funds from the World Bank (276). About 18,000 Indonesian women chose Norplant in preintroductory trials. Between approval in 1986 and January 1987 an additional 57,000 women adopted the method (85). In Thailand almost 7,000 women are using Norplant (85); in Finland about 9,000; in Sweden about 10,000 (124).

At a follow-up visit to a clinic in Brazil, a Norplant user lets other clients see that implants hardly show. (Population Council)

UNFPA is the only donor agency currently supplying Norplant to developing countries. In 1985 UNFPA shipped 12,000 sets of Norplant implants, mainly to India and the Dominican Republic. In 1986 about 38,000 sets were shipped to four countries—India, Thailand, Tunisia, and Nigeria. Shipments to India were the 2-rod Norplant-2 system for clinical trials. All other shipments were 6-capsule Norplant (245). The International Planned Parenthood Federation (IPPF) has approved Norplant for distribution to its 120 affiliated family planning associations if the countries have granted regulatory approval and if health workers have been trained.

More Nonbiodegradable Implants Being Developed

In addition to levonorgestrel, which is used in Norplant, at least 10 compounds have been tested in nonbiodegradable implants (150). Most have proved unsuitable for contraception or for delivery in implants. Several are promising, however, and clinical trials are underway (see Table 1). As of March 1987, no application had been filed with the US Food and Drug Administration (US FDA) for testing or approval for these products. The most advanced is an implant containing desogestrel, a new progestin used for several years in some oral contraceptives. The pharmaceutical firm Organon International and the Population Council are conducting clinical trials with the main metabolite of desogestrel, 3-keto desogestrel. Different lengths of a single rod are being tested in Chile and Sweden to determine release rates and duration of action (168). In addition, trials with single rods releasing about 15 µg or 30 µg per day are being conducted in China (173). The rod can be inserted in the inside or outside of the upper or lower arm. Organon International plans to develop implants with varying amounts of hormone so that a single rod will prevent pregnancy for two, three, or four years (173).

Another progestin, ST-1435, also is being used in implants (47). In recent clinical trials one capsule with 20 to 40 mg ST-1435 suppressed ovulation and prevented pregnancy in 28 women for six months (140, 141). Like Norplant and other progestin-only contraceptives, the ST-1435 implant causes irregular bleeding. Amenorrhea occurs more often with ST-1435 than with Norplant. Almost 60 percent of the 28 women did not menstruate for at least 90 days over a 12-month period. Because ST-1435 diffuses fairly rapidly through the implant membrane, a single capsule may have to be replaced every 6 to 12 months (140). The Population Council is developing a single rod implant expected to release hormones at a constant rate for two years. The organization plans to submit an application to US FDA for permission to test this implant (168).

BIODEGRADABLE IMPLANTS

Biodegradable implants deliver progestins from a carrier that gradually dissolves in body tissues. Thus the carrier never has to be removed, as with Norplant implants. Once the carrier begins to dissolve, however, it cannot be removed.

Two implants now being tested in women are:

- a polymer capsule filled with the progestin levonorgestrel and
- pellets consisting of the progestin norethindrone and small amounts of cholesterol.

Preliminary results indicate that both implants are safe and effective. Both may be available by the mid-1990s.

Capronor

Capronor, developed by the Research Triangle Institute, consists of a biodegradable capsule made of the polymer poly(ε-caprolactone) containing the progestin levonorgestrel. Current trials involve capsules that are less than 0.24 cm in diameter and either 2.5 cm or 4 cm long (202, 260). The shorter capsule contains 16 mg levonorgestrel. The longer capsule contains 26 mg levonorgestrel. In both capsules the levonorgestrel is suspended in an oily solution of ethyl oleate (97). Studies in rabbits and monkeys suggest that contraceptive protection will last at least 18 months and probably longer (260). The polymer carrier remains largely intact for 18 to 24 months and can be removed easily during that time. Then it begins to biodegrade. It is not completely absorbed for several years (260).

The first clinical trials of Capronor in women began in 1980 (202). A 2.5 cm long device releasing an average of 20 μg levonorgestrel per day suppressed ovulation in 22 of 26 women during one menstrual cycle. A 4 cm device releasing 30 to 50 μg levonorgestrel daily prevented ovulation in all 10 women using it (260). Recruiting for Phase II trials (preliminary effectiveness trials) comparing the 2.5 and 4 cm devices began in early 1987. Conducted by the US National Institute of Child Health and Human Development (US NICHD), the World Health Organization (WHO), and the Indian Council of Medical Research (ICMR), the trials will enroll between 250 and 300 women for one year (97).

Few side effects have been reported in the small, preliminary trials of Capronor. None of eight women in a US study reported bleeding between menstrual periods. The average length of the menstrual cycle was about four days shorter than before the device was inserted. No changes in blood pressure, lipids, or blood chemistry were observed (174).

Capronor is inserted under the skin in the hip or upper arm. The area is first numbed with a local anesthetic. A small incision is made in the skin, and the capsule is inserted through a special inserter (see photo, p. K-66). The polymer capsule does not cause inflammation at the insertion site (174).

Norethindrone Pellets

Small pellets are another type of biodegradable implant. The pellets were developed by Gopi Gupta while working at the Population Council (90). They are made of 15 percent pure cholesterol and 85 percent norethindrone (NET). Each pellet contains about 35 mg NET, which is released as the pellets gradually biodegrade. The pellets are quite small, each a little larger than a grain of rice. After insertion they are barely visible under the skin (226).

Preliminary trials using two, three, and four pellets have been conducted in over 100 women in four countries. With all three regimens the release of hormone was fairly constant (198, 226). The daily dose of NET and contraceptive effectiveness increased with the number of pellets:

Hormone Release Rates and Numbers of Pregnancies with Two, Three, and Four NET Pellets

No. of Pellets	Mean Daily Release (μg)	No. of Women	No. of Pregnancies
2	111 ± 20	50	3 at 6 months
3	150 ± 7	51	2 at 12 months
4	213 ± 9	30	0 at 12 months

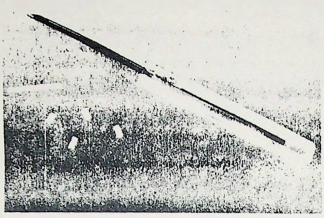
Source: PARFR (197, 198), Singh et al. (226)

The 4-pellet regimen appears to provide a high level of protection against pregnancy for at least 12 months. Thus further research will focus on this regimen.

More than half of the women using three or four NET pellets experienced irregular menstrual patterns. Intermenstrual bleeding or spotting was the most common problem. In time bleeding returned to preinsertion patterns, however. For example, among women using the 4-pellet regimen, the percentage experiencing more than five days of bleeding or spotting per menstrual cycle was 40 percent before insertion, 70 percent in the first month after insertion, and 43 percent in the sixth month after insertion (197, 198). Amenorrhea occurred in 14 percent of women by six months. The pellets relieved moderate and severe menstrual pain in most women who had experienced it previously (197, 226).

Table 3. Characteristics and Status of Biodegradable Implants as of March 1987

Delivery System	Development & Testing	Hormone	Duration of Action	Status of Animal Trials	Status of Human Trials			Estimated Availability
					Phase I	Phase II	Phase III	
Capronor (poly (ε-caprolactone) capsule)	Research Triangle Institute	Levonorgestrel	At least 18 months	Completed	Completed	To begin in 1987 in 6 countries with 250–300 women		Mid-1990s
Pellets	Population Council; Endocon, Inc.	Norethindrone	1 year	Completed	Completed using 2 pellets	Completed in 3 countries with 81 women using 3 or 4 pellets		Mid-1990s



Capronor (long capsule at left) and contraceptive pellets are both long-acting implants that dissolve in body tissue and do not need to be removed. The special inserter can be used with either.

Few women reported side effects other than irregular bleeding. Breast pain or discharge occurred in three women (4 percent). The very small amount of cholesterol in each pellet—less than 2 percent of the cholesterol in a single chicken egg—did not affect serum cholesterol levels in any of the women (198).

The pellets are inserted in the inner side of the upper arm. The insertion procedure is like that used with Capronor and can use the same inserter. After the area is numbed with local anesthetic, a 3 mm incision is made. The pellets are inserted about 3 cm under the skin. Sutures are not needed, and the wound is covered with a bandage. If the pellets are to be removed before they biodegrade, a 5 mm incision is needed. In preliminary trials pellets broke in about 5 percent of both insertions and removals. The broken pieces were not difficult to remove, however. When researchers removed pellets, they noted that fibrous tissue had developed around the pellets in most women. This had not caused any inflammation or discomfort, however, and had not interfered with release of NET (197, 198).

Plans are being made to conduct larger clinical trials with the 4-pellet regimen. A manufacturing process is being developed so that the pellets can be produced easily and inexpensively on a large scale (79, 224).

INJECTABLE MICROSPHERES AND MICROCAPSULES

Injectable microspheres and microcapsules consist of a biodegradable copolymer and one or more hormones. The many microspheres or capsules release hormones at varying rates to achieve a fairly constant daily dose, like that of implants. Depending on the formulation, a single injection of microspheres, suspended in a sterile solution, can provide contraception for one, three, or six months. Like other injectables (see pp. K-69–76), microspheres and capsules are easy to administer but, once administered, cannot be removed.

The microspheres and capsules being studied use the carrier poly(dl-lactide-co-glycolide). The polymers in this carrier have been used safely for years in biodegradable surgical sutures (25). Progestins and other hormones can be dispersed in the polymeric particle (microsphere) or contained in the core of the particle (microcapsule) (25, 147). With both systems hormone is released first by leaching or by diffusion through the carrier and later by erosion of the carrier.

The size of microspheres or capsules and the amount of hormone they contain, as well as their quantity, largely determine the daily dose of hormone. Smaller particles release hormone faster and so have a shorter duration of action. Among particles of the same size, those with more hormone and less carrier release hormone faster (25, 92). A 3-month dose of injectable norethindrone microspheres usually contains particles consisting of 50 percent hormone and ranging in size from .06 to 0.1 mm in diameter (24). Sterilization of microspheres or capsules by gamma radiation slightly increases hormone release (92).

For an injection, microspheres are loaded into a syringe. Then a sterile suspension fluid is drawn into the syringe. A 3-month formulation of norethindrone microspheres, for example, contains about 2½ cc of fluid and is injected into the buttocks with a 21 gauge needle (22) (see photo, p. K-68). The syringe must be shaken just before an injection. This prevents the larger, heavier spheres from packing at the bottom of the syringe (205). Earlier formulations composed of 80 percent polymer and 20 percent hormone were very dense, and researchers were not always able to inject all the microspheres (24). Microspheres of half polymer and half hormone have eliminated this problem, decreased the amount of material injected, and reduced discomfort from the injection (22).

In addition to contraception, microspheres are being used to deliver drugs to treat medical conditions. In the US, for example, a small trial is underway studying testosterone microspheres in men with abnormally low production of testosterone (146). In Europe several pharmaceutical companies are testing microspheres containing luteinizing hormone releasing hormone (LHRH) antagonists to treat endometriosis and prostate cancer (22). Microspheres with natural estrogen are now being tested in animals. These microspheres could provide estrogen replacement therapy for postmenopausal women (22).

For contraception in women, injectable microspheres are being tested with various hormones (see Table 6). Most promising are microspheres with either norethindrone or a new progestin, norgestimate. Microspheres also are being considered for male contraception. Possible formulations are testosterone alone or testosterone combined with LHRH analogues (146, 280).

Norethindrone Microspheres

Injectable microspheres containing norethindrone (NET) have been tested in almost 200 women. Results are promising. In short-term clinical trials different formulations of 3-month injections have prevented pregnancy and caused very few side effects other than menstrual irregularities. Norethindrone microspheres were developed by Lee Beck and Danny Lewis of the Stolle Research and Development Corporation with support from the Program for Applied Research in Fertility Regulation (PARFR). Family Health International is conducting larger clinical trials in four countries to test two formulations of a 3-month injection—with 65 and 100 mg NET. Trials of the 65 mg injection in about 1,200 women have been approved by the US Food and Drug Administration and will begin in 1987 (22, 44).

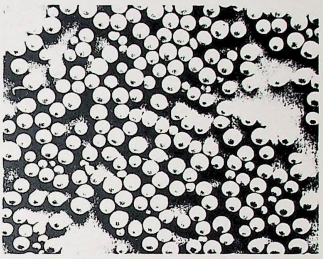
NET microspheres prevent pregnancy with doses comparable to those in combined oral contraceptives. A 3-month injection containing a total of 75 mg NET releases on average 0.48 mg NET per day. A 1-month injection containing 100 mg NET releases 0.66 mg per day (26). By comparison, the daily dose of NET used in some combined oral contraceptives ranges from 0.5 to 1 mg in various formulations (102). In initial trials none of the 10 women receiving the 75 or 100 mg 3-month injections ovulated during treatment (26). In the second phase of trials, after more than 300 woman-months of observation, one pregnancy has occurred among 60 women receiving 65 mg injections. None has occurred among 65 women receiving 100 mg injections (44).

A 6-month injection with 200 mg NET looks less promising. When it was tested in 10 women, there were no pregnancies during the 24-week period, but 2 of 10 women appeared to ovulate before six months, and one woman conceived 26 weeks after the injection (205).

Irregular menstrual bleeding is the only common side effect of NET microspheres. Amenorrhea or long cycles with persistent spotting are the most common patterns (205). Among 10 women each receiving a 3-month injection, the total number of days per cycle with bleeding or spotting ranged from 5 to 9 with the 75 mg injection and from 8 to 11 with the 100 mg injection (24, 26).

Other side effects are rare. Among 115 women, only a few complained of mild headaches or nausea, and it is not clear that these were caused by the injection (44, 206). There have been no infections at the injection site. No changes have been observed in blood pressure, hemoglobin, serum lipoproteins, triglycerides, or glucose metabolism (24, 44). The contraceptive effect of the microspheres wears off rapidly. Most women ovulate within two months after the end of the 3- or 6-month injection interval (44, 205).

Other formulations of NET microspheres are being studied. A one-month injection with 15 or 30 mg NET has been tested in about 30 women in Mexico. Also, animal studies have been completed with various formulations of one- and three-month injections of NET and the synthetic estrogen ethinyl estradiol. In animals these formulations caused very little irregular bleeding and very slight endo-



In clinical trials norethindrone microspheres prevent pregnancy for three months. Microspheres are .06 to 0.1 mm in diameter. The smaller microspheres release hormone faster. (Stolle Research Corporation)

Table 4. Characteristics and Status of Injectable Microsphere and Microcapsule Contraceptives as of March 1987

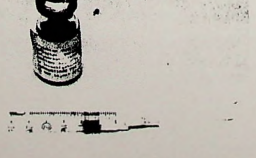
Hormone	Development & Testing	Duration of Action	Status of Animal Trials	Status of Human Trials			Estimated Availability
				Phase I	Phase II	Phase III	
Norethindrone (microspheres)	Stolle Research & Development Corporation, Family Health International	3 months	Completed	Completed	Underway at 8 sites in US, Mexico, Chile & Italy with 65 & 100 mg formulations in 160 women	Planned for 1987 with 65 mg formulation in 1,200 women	Early 1990s
		6 months	Completed	Completed in Mexico & US with 200 mg formulation			No sooner than late 1990s
		1 month	Completed	Completed in Mexico with 15 mg & 30 mg formulations in 30 women			Mid-1990s
Norgestimate (microcapsules)	Ortho Pharmaceutical, Contraceptive Research & Development (CONRAD)	3 months	Completed	Underway in US with 50 mg formulation			Mid-1990s
Progesterone (microcapsules)	Stolle Research & Development Corporation	3 months	Completed	Underway in Chile & US			No sooner than late 1990s
Levonorgestrel (microspheres)	Stolle Research & Development Corporation	3 months	Completed	Approved to begin in US			No sooner than late 1990s
Norethindrone (NET) & ethinyl estradiol (EE) (microspheres)	Stolle Research & Development Corporation	3 months	Completed	Approved to begin in US with 30 mg NET & 5 mg EE			No sooner than late 1990s

metrial changes. This suggests that the combination injection may cause less irregular bleeding in women than injections alone. Initial trials in women of a 3-month injection have been approved and are planned for 1987. This injection will contain about 30 mg NET and about 1.3 mg ethinyl estradiol (22).

Microcapsules with Various Other Hormones

Research is underway on microcapsules containing other hormones. Animal studies with Ortho Pharmaceutical's new progestin, norgestimate, suggest that it will cause less spotting than other progestins. In six baboons microcapsules containing 50 mg norgestimate suppressed ovulation for 90 to 120 days (92, 93). Endometrial biopsies on these animals showed hormonal effects like those occurring naturally in the postovulatory phase of the menstrual cycle (257). Spotting did not occur in any of the animals (92, 93). Thus norgestimate may cause less irregular bleeding in women than other progestins that have a more marked effect on the endometrium. Norgestimate is a more potent progestin than NET and has no androgenic side effects such as hair growth and acne (93). Therefore it is likely to be highly effective and also popular with women. Initial trials of a 3-month injection with 50 mg norgestimate are underway in the US (91).

Preliminary trials of microcapsules containing the natural hormone progesterone were carried out in 1986 in Chile and the US (146). Progesterone microcapsules are intended specifically as a contraceptive for lactating women to eliminate any possible effects of synthetic progestins on breast milk production or composition or on the nursing infant. The trials involved about 10 women receiving a 3-month injection with 275 mg progesterone (146). This dose appears high compared with other microsphere and microcapsule formulations because progesterone is less potent than synthetic hormones. Preliminary results showed that the microcapsules release a smaller than expected amount of progesterone per day. Plans are underway to increase the progesterone in the microcapsules so that the daily release rate will be about 20 percent higher. Initial trials of the modified microcapsules are planned for 1987. Another way to deliver progesterone that is being considered is an injection of a micronized preparation of pure progesterone—that is, a crystalline form ground to a fine powder. One injection would be effective for a month.



Norethindrone microspheres offer the convenience of an injection without the large initial burst of hormone that occurs with currently available injectables. For clinical trials microspheres are supplied in a sterile syringe. Fluid is drawn from the vial, and the syringe is shaken just before the injection is given.

In China researchers have been testing monthly injections of microcapsules containing various doses of the progestin megestrol acetate and the estrogen estradiol valerate. The lowest side effects occurred with a monthly dose of 15 mg megestrol acetate and 5 mg estradiol valerate. With this regimen the pregnancy rate was 1.1 per 100 woman-years in a study involving 444 women. Spotting occurred in only 3 percent of menstrual cycles, and only 9 percent of cycles were either longer than 36 days or shorter than 20 days (100).

VAGINAL RINGS

Vaginal rings are different from the other new long-acting hormonal methods. Although, like the others, they slowly release hormone, vaginal rings are not injected or placed under the skin. Instead, a woman simply places the ring in her vagina and leaves it there. She can remove it at any time.

Levonorgestrel Rings

Research is most advanced on a ring developed by the World Health Organization (WHO) that releases about 20 µg levonorgestrel per day. This ring is designed to stay in the vagina for three months. It consists of an inner core containing 6 mg levonorgestrel mixed with Silastic and an outer shell of Silastic alone. The ring's overall diameter is 55.6 mm; its cross-sectional diameter, 9.5 mm. The ring prevents ovulation in at least half of cycles (292, 302) and also thickens cervical mucus, preventing sperm from entering the uterus (272).

The levonorgestrel ring is less effective than implants or injectables. In a multicenter one-year trial involving about 1,000 women, there were 25 pregnancies, for a rate of 3.5 per 100 woman-years (260). Like other progestin-only methods, vaginal rings cause irregular bleeding, and this accounted for most discontinuations. About 8 percent of the women stopped using the ring because of vaginal discharge, irritation, or infection, and about 4 percent, because of expulsion. Expulsion is most likely when women squat to defecate (97).

WHO has applied for approval of the levonorgestrel ring in the UK. Approval is being postponed until machinery for manufacturing the rings is completed and the manufactured rings are shown to release levonorgestrel at the same rate as the handmade rings. The manufacturing process should be final by late 1987. Approval is expected in 1988 (97).

Progesterone Ring

Another ring contains the natural hormone progesterone. It is designed especially for breast-feeding women so that they will not be exposed to synthetic hormones that might affect the composition or quantity of breast milk. Like the levonorgestrel ring, the progesterone ring can remain in the vagina for three months. Currently, WHO and the Population Council are testing rings releasing 5 or 10 mg progesterone per day (260). According to a small study in Chile, growth of infants and duration of breast-feeding were very similar when infants of women using the rings or TCu-200 IUDs were compared. Bleeding and/or spotting

Table 5. Characteristics and Status of Vaginal Rings as of March 1987

Hormone	Development & Testing	Duration of Action	Status of Animal Trials	Status of Human Trials			Estimated Availability
				Phase I	Phase II	Phase III	
Levonorgestrel	WHO HRP	3 months	Completed	Completed	Completed	Completed	Approval in UK pending, expected in 1988
Progesterone	WHO HRP, Population Council	3 months	Completed	Completed	Ongoing		Early 1990s

WHO HRP = World Health Organization Human Reproduction Program

for more than six days per 30-day interval occurred more often among the IUD users (55).

Combined Progestin-Estrogen Rings

The Population Council is working on several rings that deliver both progestins and estrogens. These rings are intended to be kept in the vagina for three weeks at a time and removed for one week to allow monthly bleeding. Preliminary studies in about 10 women showed that a ring releasing 400 μg norethindrone acetate and 40 μg ethinyl estradiol daily stopped ovulation in all women and caused very little irregular bleeding. This ring is now being changed to reduce the daily release of ethinyl estradiol. Human trials of the new version are planned for 1987. The Population Council also plans to test vaginal rings with two other progestins, ST-1435 and levonorgestrel acetate, alone and combined with ethinyl estradiol (168).

Advantages and Disadvantages

To date, few women have tried vaginal rings. Thus, as with many of the other new methods, it is not clear how popular they will be. In a British trial 26 of 27 women using the levonorgestrel ring said that they preferred it to oral contraceptives, condoms, and the diaphragm, primarily because it was so easy to use (293). Earlier trials in eight countries found that discontinuation rates were similar for oral contraceptives and a ring of levonorgestrel and ethinyl estradiol. Significantly more discontinuations among ring users were for method-related problems, however, especially difficulties or "unpleasantness" with inserting or removing the ring (297).

Two vaginal rings (shown actual size) release hormone for 3 months. The upper ring contains norgestrel; the lower, progesterone.

Compared with the other new long-acting methods, the big advantage of the vaginal ring is that a woman can put it in and take it out herself. This means that she can start and stop the method easily, without help from a health worker. It also means that rings can be distributed through commercial channels and community-based distribution programs more easily than some of the other new methods.

Unlike barrier methods, vaginal rings do not have to be inserted just before intercourse. In fact, they will not work if used only during intercourse. A woman can remove the ring before intercourse, however. In early trials one-fourth of users removed the rings at least some of the time, often because their partners could feel them (286, 297). Removing the ring for a short period—as long as 2 hours for the progesterone ring and possibly as long as 24 hours for the levonorgestrel ring—will not decrease effectiveness (168). Leaving them out longer may increase the risk of pregnancy (55, 97).

The vaginal rings appear to have several possible disadvantages. Women who dislike touching their genitals may not like inserting and removing the rings, as earlier studies indicated. Also, the preliminary data on the current version of the levonorgestrel ring suggest that it is less effective than other hormonal methods, voluntary sterilization, or the more effective IUDs.

LONG-ACTING INJECTABLES

Two long-acting injectables are widely available—depot medroxyprogesterone acetate (DMPA; trade name Depo-Provera; the Upjohn Company) and norethindrone enanthate (NET EN; trade name Noristerat; Schering AG). Both are highly effective, reversible methods. DMPA is approved for use as a contraceptive in more than 90 countries; NET EN, in more than 40. Although injectables have proved very popular, controversies—particularly about DMPA—have limited their availability in some areas. Questions have been raised about long-term health risks, especially cancer, but new studies are for the most part reassuring. Some questions concerning cancer remain, however. Research continues on both injectables.

The synthetic hormones used in both injectables were developed in the 1950s. The progestin medroxyprogester-

New Leaders in Contraceptive Research and Development

The leading roles in contraceptive research and development are changing. For a combination of reasons, some pharmaceutical companies are increasingly reluctant to initiate contraceptive research and development. More and more, nonprofit organizations and government agencies are taking the lead, and pharmaceutical companies are collaborating with them. Regardless of who takes the lead, however, developing a new drug remains a long, complex, and costly process.

Drug Regulation

Over the last several decades the process of contraceptive testing has become increasingly standardized to meet the requirements of government drug regulations. Many countries require specific series of animal and human tests to establish safety and efficacy before a drug can be made available (118). Often these requirements are modeled on those of the US Food and Drug Administration (US FDA). The US FDA requires that steroid contraceptives be tested in three animal species—rats for 2 years, beagle dogs for 7 years, and monkeys for 10 years. Human trials are usually carried out in three phases with increasing numbers of volunteers (see note, Table 1, p. K-59). Human trials can start and progress from one phase to the next only after animal trials have successfully reached certain stages.

While adequate testing is essential, the cost and time spent on the tests now required has helped discourage pharmaceutical manufacturers from developing new contraceptives. A 7-year dog study or a 10-year monkey study can cost between $500,000 and $2 million (US) (60). The annual cost of early, Phase I human trials in the US is about $70,000 per person (31). Furthermore, the lengthy research and development process limits profits. In the US, for instance, patents now protect new compounds for 22 years. If most of those years are taken up in testing, little time is left for exclusive marketing. In hopes of shortening testing, many developers are focusing on new delivery systems for compounds already approved—for example, the compounds now used in oral contraceptives. Also, most new contraceptives are intended for international distribution. Thus researchers must meet the differing regulations governing clinical trials in many different countries (95, 118, 160). This, too, adds to costs.

Other Impediments

Concerns over legal liability and insurance costs, especially in the US, also have discouraged some pharmaceutical manufacturers. For example, in 1986 the G.D. Searle Company withdrew the Cu-7 IUD from the market because responding to a mounting number of law suits, even though the company usually won, was very costly. Today, only one IUD, the Progestasert, is still marketed in the US even though IUDs are a safe and effective contraceptive method. Also in 1986, the US Supreme Court affirmed an award of $4.7 million (US) for a birth defect allegedly caused by spermicidal jelly—even though the weight of scientific evidence showed that the spermicide was not to blame. Manufacturers cannot afford to risk the high cost of law suits – win or lose—over a product that generates little profit. Contraceptives may generate little profit if the amount of sales is small, as with spermicides, or if the method is low-cost and long-acting, as with IUDs.

Also in the US, contraceptive developers are having difficulty finding product liability insurance. As a result, clinical testing in the US sometimes must be delayed for several years, as in the case of the biodegradable implant Capronor, or held to the minimum required by the US FDA, as in the case of Norplant (8, 15).

Even when the required testing is finished, political controversy can delay regulatory approval. Some opponents of DMPA have made a political issue of fears that women would be given injectables without their knowledge or full understanding. Controversy over this issue lengthened US FDA deliberations over Depo-Provera and delayed approval in the UK until 1984 (196).

The Role of Nonprofit Organizations

While interest declines among pharmaceutical manufacturers, a handful of nonprofit organizations are emphasizing contraceptive research and development. In 1985 eight such organizations spent more than $40 million (US) working on 23 new products (15).

Nonprofit organizations currently involved in contraceptive research include the Human Reproduction Program of the World Health Organization (WHO); government agencies, such as the Center for Population Research of the US National Institute of Child Health and Human Development (US NICHD) and the Indian Council of Medical Research (ICMR); and private research organizations usually receiving both public and private funds, such as the Contraceptive Research and Development Project (CONRAD), the Population Council, and Family Health International (FHI). Many of these organizations receive support from the US Agency for International Development. These organizations often collaborate with each other, with the pharmaceutical industry, and with other independent research institutions such as university centers (16).

Nonprofit research organizations face the same problems as pharmaceutical manufacturers in meeting national regulations and obtaining US liability insurance. In addition, because they often have small budgets and no distribution systems, nonprofit organizations must develop and maintain close working relationships with governments and manufacturers.

Calls are increasing for a simplified, more flexible approach to drug regulation (53, 142, 252). In early 1987 WHO convened a meeting to discuss new guidelines for toxicological studies of steroidal contraceptives. The draft guidelines stress a flexible approach, in which the characteristics of the drug govern the design of animal studies and clinical trials. They also stress the need for systematic, long-term postmarketing surveillance. WHO has been invited to present the proposed guidelines to US FDA. Meanwhile, reform of liability insurance in the US is being proposed (8, 244). Until such changes are made, however, new methods of contraception will still take many years to reach the public.

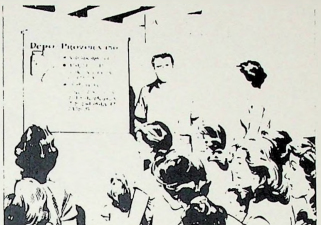
one acetate (MPA), the hormone in DMPA, is derived from the natural hormone progesterone. DMPA is prepared in a microcrystalline suspension. Thus the hormone is not absorbed immediately after an injection. The usual dose of DMPA is 150 mg every three months. Six-month regimens of 250 to 450 mg DMPA are less widely used. The progestin NET EN is derived from testosterone. NET EN is prepared in an oily solution. A 200 mg injection is effective for up to 12 weeks.

Effectiveness

Both DMPA and NET EN are highly effective contraceptives. With the standard regimens, pregnancy rates are usually lower than one per 100 woman-years for DMPA and two per 100 woman-years for NET-EN (see **Population Reports,** *Long-Acting Progestins—Promise and Prospects*, K-2, May 1983). Unplanned pregnancies are rare because both injectables suppress ovulation in the great majority of cycles and because a woman needs only to obtain the next injection at the right time in order to assure continued effectiveness.

Several different regimens of DMPA have been used. In a recent randomized trial of two DMPA doses, none of the women receiving the standard 150 mg dose conceived, but the pregnancy rate among women receiving 100 mg every three months was 0.44 per 100 woman-years (268). With higher doses and a longer injection interval—250 to 450 mg every six months—pregnancy rates have ranged from 0 to 3.6 per 100 woman-years (150, 162, 200, 214).

NET EN is given in both 2-month and 12-week regimens. With the 12-week regimen, the first three 200 mg injections are given at 8-week intervals, and subsequent injections are given at 12-week intervals. The 2-month regimen is markedly more effective. Two-year cumulative life-table pregnancy rates with the 2-month regimen range from 0.4 to 1.8 per 100 women (112, 266, 271). In contrast, with the 12-week regimen 2-year rates as high as 6.6 per 100 women have been reported (112, 271). The World Health Organization (WHO) now recommends that NET EN be given at intervals no shorter than 46 days and no longer than 74 days (about 7 to 10 weeks) (67). Schering AG, manufacturer of NET EN, notes that contraceptive protection is not adequate if more than 12 weeks passes between injections



A pamphlet from the Philippines shows interested women learning about Depo-Provera (DMPA). Depo-Provera is the most popular long-acting progestin contraceptive, used by nearly 4 million. The pamphlet was prepared by Kabalikat ng Pamilyang Pilipino.

and recommends the 2-month regimen if the 12 week regimen is not possible (61).

Administering injectables in the first week of the menstrual cycle provides the greatest protection against pregnancy. It also ensures that the woman is not already pregnant at the time of the injection. Injections after the first week may not prevent ovulation in that cycle, increasing the risk of pregnancy (227). In a Thai study involving almost 8,000 women, the pregnancy rate after one injection among those who received DMPA in the first eight days of their cycles was 1.6 per 100 women compared with 6.2 for those who received the injection between the ninth and twenty-eighth days of their cycles (84).

There are few known contraindications to progestin-only injectables. WHO recommends that women should not use injectables if they are pregnant, have cancer of the breast or genital tract, or have abnormal uterine bleeding (259). WHO also recommends that, before giving injectables, health workers carefully consider the standard contraindications to combined estrogen-progestin oral contraceptives, even though it is not certain how applicable

Table 6. Characteristics and Status of Long-Acting Injectables as of March 1987

Hormone	Development & Testing	Duration of Action	Status of Animal Trials	Status of Human Trials			Availability
				Phase I	Phase II	Phase III	
DMPA (150 mg depot medroxyprogesterone acetate)	Upjohn Company	3 months	Completed	Completed	Completed	Completed	Approved in over 90 countries
NET EN (200 mg norethindrone enanthate)	Schering AG	2 months or 12 weeks	Completed	Completed	Completed	Completed	Approved in over 40 countries
HRP002 (6.25, 12.5, and 25 mg levonorgestrel butanoate)	WHO HRP	3 months	Underway	Completed in 3 sites in 50 women	Will begin in mid-1987		Expected to be available for pre-registration studies in 1992
HRP011 (20, 40, and 60 mg levonorgestrel 3-oxime cyclopentyl carboxylate	WHO HRP	2 months	Completed	Underway in 3 sites in 30 women	Will begin in early 1988		Mid-1990s

WHO HRP = World Health Organization Human Reproduction Program

the [illegible]se. In addition, WHO advises that women with diabetes or a history of diabetes during pregnancy should be followed carefully, since some laboratory tests have shown that DMPA alters carbohydrate metabolism (259).

Menstrual Changes

Changes in menstrual patterns are the most common and troublesome side effect of DMPA and NET EN. Over two-thirds of women using DMPA and over one-half of women using NET EN have no regular cycles in the first year of use (10, 37, 43, 240, 267). Women may stop menstruating altogether (amenorrhea), have very irregular bleeding or spotting, or experience changes in the duration or amount of blood flow. Of these, amenorrhea is the most common and occurs more often with DMPA. During the first year of use about 55 percent of DMPA users do not menstruate for 90 days or more, compared with about 30 percent of NET EN users (41, 130, 271). As women continue using injectables, fewer experience intermenstrual bleeding and spotting, and more experience amenorrhea (271).

Very heavy or prolonged bleeding, a potential health threat, is uncommon (76, 130, 150, 272). In a WHO multicenter trial, for example, only 6 of 1,200 women (0.5 percent) needed treatment for heavy bleeding in almost 14,000 women-months of use (272). Similarly, in a 12-month field trial in Pakistan, only one of 2,147 women required curettage for prolonged bleeding (110).

Generally, amenorrhea and light bleeding or spotting do not require any medical treatment. Most family planning providers find that they can allay women's concerns by counseling them before an injection and reassuring them if menstrual changes occur. Oral contraceptives or supplemental estrogens to regularize menstrual bleeding are not prescribed routinely (76, 259). Very heavy or prolonged bleeding, however, does require medical attention. WHO recommends either (1) one combined oral contraceptive daily for 14 days or (2) an intramuscular injection of a synthetic estrogen—5 mg estradiol cypionate or estradiol valerate (261).

More women stop using injectables because of menstrual disturbances than for any other reason. In recent trials 6 to 30 percent of women discontinued the method in the first year because of changes in bleeding patterns (112, 130, 199, 251, 266, 270). Discontinuation rates vary widely, perhaps because of different cultural and religious attitudes toward menstrual disturbances or because of the varying availability of counseling and follow-up.

Reproductive Effects

Neither DMPA nor NET EN appears to have any permanent effect on fertility. With both injectables, however, women may not ovulate or conceive for several months after discontinuation. This delay has caused concerns about reversibility, particularly with DMPA. Because of fears that DMPA might cause permanent infertility, some national family planning programs do not allow women to use DMPA unless they have had at least one child (133).

The contraceptive effect of DMPA often lasts well beyond three months. In the largest study to date the median time to conceive after a DMPA injection was 9 months, or 5½ months after the end of the presumed duration of effectiveness. Despite this initial delay, over 60 percent of former DMPA users became pregnant within 12 months, and over 90 percent, within 24 months. These rates are similar to those among former users of oral contraceptives or IUDs (176). How long a woman has used DMPA and whether she has already had a child do not affect the speed with which fertility returns (159, 176, 215).

With NET EN, return of fertility also can be delayed. In a recent study of 69 women who stopped using NET EN to become pregnant and who were followed for a year, average time to conception was longer than among 92 former TCu-200 IUD users. After one year, however, 73 percent of former NET EN users and 84 percent of former IUD users had conceived. The difference is not statistically significant (289). In an earlier study of 40 women, 78 percent conceived within 12 months after the last injection (74). Most women ovulate within four months after discontinuation (72, 77, 253, 255). As with DMPA, duration of use does not affect how quickly fertility returns (74).

Questions have been raised about possible harmful effects on children exposed to injected progestin contraceptives either in utero or during breast-feeding. Several studies in the 1960s reported no increase in birth defects or prematurity when pregnant women were inadvertently given contraceptive doses of injectable progestins (13, 161, 247). In a recent study of Thai children by Tieng Pard-

What Providers Should Know About Long-Acting Injectables

1. The standard regimens are 150 mg DMPA every three months and 200 mg NET EN every two months or 12 weeks.
2. Injectables are very effective. Failure rates are usually less than one or two percent.
3. The weight of available evidence suggests no increased risk of cancer with DMPA. Whether NET EN affects risks of cancer in women has not been studied.
4. Injectables change menstrual bleeding patterns. From 30 to 60 percent of users develop amenorrhea.
5. Medical treatment for menstrual irregularities is not necessary unless a woman is bleeding very heavily. This complication is quite rare.
6. Women may be infertile for four to nine months or more after an injection. Fertility returns eventually, however.
7. Injectables do not seem to interfere with breast-feeding. The small amounts of hormone in breast milk do not appear to harm the infant.
8. Before receiving an injection, women must be aware that any side effects may persist for the 2- or 3-month period of effectiveness and that return of fertility may be delayed.
9. If possible, injectables should be given during the first week of the menstrual cycle to insure that the woman is not already pregnant.
10. Injectables have beneficial health effects. They often increase blood iron levels, and they appear to help protect against pelvic inflammatory disease and ovarian and endometrial cancer.

Jhansong and colleagues, however, children of former users of DMPA were two times more likely to have reproductive birth defects and about five times more likely to have chromosomal abnormalities than children of women who used no contraception. Interpreting these results is difficult, in part because the number of cases is small and in some cases exposure long preceded pregnancy (177). Preliminary analysis from a study in Israel, involving nearly 200 adolescents who were exposed in utero to medroxyprogesterone acetate and over 950 controls, found no evidence of retarded or precocious development or any disturbance in sexual development, sexual behavior, or growth among those exposed (101). These studies in Thailand and Israel, supported by WHO and Family Health International (FHI), are continuing to look at children exposed in utero to DMPA, medroxyprogesterone acetate (MPA), or oral contraceptives (261).

The very small amount of hormone transmitted in breast milk appears to have no effects on children even when followed up to 10 years (127, 129, 247). A Chilean study found that a higher percentage of DMPA users' four-year-old children weighed below average than did nonusers' children. The researchers attributed this difference to factors other than DMPA use, since the mothers using DMPA were older, had more children, and had breast-fed their children longer (127).

Cardiovascular Effects

Unlike oral contraceptives that contain estrogen, DMPA and NET EN appear to have little effect on the cardiovascular system. There have been very few reports of blood clots or other cardiovascular complications in women using injectables, but adequate epidemiologic studies have not yet been conducted. In the laboratory most studies find no change in blood pressure or in the coagulation and fibrinolytic systems that affect blood clotting (111, 150, 258).

Effects on lipid metabolism are less clear since long-term studies are not finished. Most reports find either no change in total cholesterol and triglycerides or a decrease, a possibly beneficial effect (11, 12, 63, 88, 150, 167, 242, 262). In contrast, a few studies report an increase in cholesterol with longer use of DMPA (149) or a decrease in high-density lipoproteins (HDL), both possibly adverse effects (128, 138). The only study involving NET EN also found a decrease in HDL (73). Because NET EN is chemically similar to testosterone, it is likely that it would reduce HDL levels slightly. Whether the small decreases in HDL sometimes seen in women using injectables have any clinical importance is not certain. WHO trials are underway in five countries to measure lipid metabolism in women using DMPA and NET EN for short and long periods (260).

Cancer

Questions about whether long-acting injectables cause cancer have aroused controversy. This is the main reason that DMPA has not been approved for contraceptive use in the US. These questions have arisen because (1) two species of laboratory animals—beagle dogs and rhesus monkeys—given large doses of DMPA or NET EN, usually for long periods, have developed benign and malignant tumors of the breast or endometrium (lining of the uterus) (61, 75, 247, 264) and (2) until recently human studies have been limited. Questions about the relevance of animal studies to humans are still unresolved (2, 62, 70, 104, 264, 272).

A pamphlet from the Sierra Leone Home Economics Association reminds women that DMPA works for three months.

Two recent studies of women, however, provide some reassurance that DMPA does not increase the risk of several types of cancer. WHO conducted a case-control study involving over 1,500 cases and over 5,800 controls in Kenya, Mexico, and Thailand. The US Centers for Disease Control and other organizations conducted a smaller study in Costa Rica involving over 700 women with breast cancer, invasive cervical cancer, or cervical carcinoma in situ and over 760 controls. Like other epidemiological and clinical research in the US, Canada, and Thailand (66, 86, 148, 163), the WHO case-control study found no link between DMPA use and cancer of the breast, endometrium, ovary, or liver (263). In fact, like oral contraceptives, DMPA may help protect against cancers of the ovary and endometrium (see Table 7).

The Costa Rican study found a two-fold greater risk of breast cancer among former DMPA users than among

Table 7. Risks of Various Cancers and DMPA Use, World Health Organization 3-Country Case-Control Study, 1986

Site of Cancer	No. of Cases Who Used DMPA/ All Cases (%)	No. of Controls Who Used DMPA/All Controls (%)	Relative Risk for Women Who Have Ever Used DMPA*
Breast	39/427 (9)	557/5,951 (9)	1.0
Cervix	126/920 (14)	545/5,833 (9)	1.2
Ovary	7/105 (7)	74/637 (12)	0.7
Endometrium	1/52 (2)	30/316 (9)	0.3
Liver	7/57 (12)	14/290 (12)	1.0

*Adjusted for center and for factors known to affect cancer risk. None of these relative risks is significantly different from 1.0.

Source: World Health Organization (236)

nonusers—a statistically significant difference. The researchers regard these results as inconclusive, however. The number of cases is small—only 19 women with breast cancer had ever used DMPA. Furthermore, there is no indication that risk increased with duration of use, as might be expected if DMPA caused breast cancer (143).

In the WHO study the risk of invasive cervical cancer appeared to be slightly higher for former DMPA users than for controls, but the difference was not statistically significant. The study found that women younger than 36 who had used DMPA for more than four years were two times more likely to develop cervical cancer than controls younger than 36. Interpreting this finding is difficult because the number of cases is small (263). Furthermore, the Costa Rican study found no increased risk of either invasive cervical cancer or cervical carcinoma in situ among former DMPA users of any age or with any duration of use (171, 172). While both studies were able to control for some variables known to influence risk of cervical cancer—the woman's age at first intercourse and the number of sexual partners—neither took account of other important influences—the sexual behavior of the women's partners or, in the WHO study, smoking (171, 172, 263).

Beneficial Effects

Like oral contraceptives, injectables have several beneficial effects in addition to preventing unplanned pregnancy. Hemoglobin levels often increase in women using DMPA or NET EN (42, 107, 262). This may help to prevent anemia, a common problem among women in developing countries. In addition, some women with sickle-cell disease have less pain and fewer abnormal red blood cells while using DMPA or other steroid hormones (38, 250). DMPA also appears to protect against some reproductive tract infections. According to a study of more than 900 women with PID and more than 600 matched controls, DMPA users were half as likely as nonusers to develop pelvic inflammatory disease, a major cause of infertility (83). Preliminary reports also suggest that DMPA protects against vulvovaginal candidiasis, a fungal infection (54). As noted, DMPA also may lower the risk of ovarian and endometrial cancer.

Continuing Controversy Over DMPA

DMPA has been the subject of debate for many years. On one hand, critics argue that DMPA is unsafe because it causes cancer in some laboratory animals and because not enough is known to rule out long-term risks to women. They also are concerned that injectables—because they are so easy to administer—may be given to women without proper precautions and full informed consent (106, 145). On the other hand, supporters of DMPA point out that epidemiological and clinical studies provide no clear proof of increased risk of cancer or other harmful effects among DMPA users and that the relevance of animal tests to humans is uncertain. In addition, they argue, the known benefits of DMPA outweigh any plausible risks as yet undetected (27, 259).

The ongoing debate has prevented the marketing of DMPA as a contraceptive in the US. In 1967 the Upjohn Company first applied to the US Food and Drug Administration (US FDA) for approval to market DMPA as a contraceptive. Eleven years later, in 1978, the US FDA formally denied approval even though its own Obstetrics and

Tests Underway on New Long-Acting Ester Injectables

A 12-year collaboration between the World Health Organization (WHO), the US National Institute of Child Health and Human Development (US NICHD), and scientists throughout the world has led to several new injectable compounds that may prevent pregnancy for two or three months.

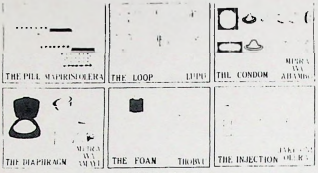
In 1975 WHO convened a group of chemists and biologists to begin the development of new contraceptive steroids. Research focused on two progestins—norethindrone (NET) and levonorgestrel—that had already been shown to be safe and effective in humans. The scientists synthesized over 230 esters derived from NET or levonorgestrel. (An ester is a combination of a steroid and an acid.) US NICHD then tested these compounds in animals. Four compounds, all derived from levonorgestrel, were selected for further testing because they consistently inhibited ovulation in animals and also appeared to be long-acting (99).

The WHO Human Reproduction Program is conducting studies of two of the four new compounds in women to find the lowest effective dose (31) (see Table 6). Trials with one compound—designated HRP002—suggest that a 20 mg dose will prevent ovulation for three months (260). Preliminary effectiveness trials are planned to begin in 1987 (97).

The appropriate dose for the second compound, HRP011, has not yet been established. This compound is chemically similar to another progestin, norgestimate, that does not cause marked endometrial or menstrual changes in animals (see p. K-68). WHO plans to begin small effectiveness trials of HRP011 in women, which will determine whether it will have less effect on bleeding patterns than DMPA and NET EN (97). Initial studies of HRP011 in a small number of women in the US are being planned for late 1987 (31).

The Contraceptive Development Branch of US NICHD has completed 2-year toxicology studies of HRP011. Studies in rats and monkeys with low, intermediate, and high doses—up to 50 times the human dose—show no harmful effects (31).

These new compounds have several important advantages over existing injectables. Because of the chemical properties of esters, the new injectables are released from the injection site at a fairly constant rate, without the initial high release that occurs with DMPA and NET EN. In addition, unlike the injectable microspheres, which also have fairly constant release rates, the new injectables can be administered in a simple aqueous microcrystalline suspension like that used for DMPA. Thus they can be manufactured easily and inexpensively. Like DMPA and NET EN, they will be administered with a simple injection. Thus many different types of health workers could administer these new contraceptives without special training.



Injectable contraception is one of several child-spacing methods in Malawi. Because many health workers know how to give injections, this method can be easily and widely offered.

Gynecology Advisory Committee had twice recommended approval for certain groups of US women. In 1983 a Public Board of Inquiry, especially convened at the request of the Upjohn Company, conducted hearings to reconsider the US FDA's decision and make a recommendation to the Commissioner of the agency. The Board consisted of three scientists jointly selected by Upjohn and the US FDA. In late 1984 the Board released its conclusions. Two of the three members concluded that there was insufficient evidence to prove that DMPA was safe for general marketing in the US (254). The third member recommended that DMPA be approved for use by women who could not use other methods (209). To date, the Commissioner of the US FDA has not acted on these recommendations, and the future of DMPA in the US remains uncertain. In 1986 the Upjohn Company reopened the issue by submitting new data on the safety of DMPA, including the WHO study results on cancer. Upjohn plans to submit a new application for approval of DMPA (59).

Since 1980 regulatory agencies in Sweden, the UK, France, and West Germany have approved DMPA for contraception (246). Also since 1980, several national and international scientific groups have endorsed DMPA, including the Toxicology Review Panel of the WHO Special Programme of Research, Development and Research Training in Human Reproduction (the Human Reproduction Program) (259) and the International Medical Advisory Panel of the International Planned Parenthood Federation (120). Currently, the US Agency for International Development does not distribute DMPA because it is not approved for contraceptive use by the US FDA. International donors are providing DMPA and NET EN to family planning programs in countries where these injectables have been approved (see p. K-78).

MONTHLY INJECTABLES

Monthly injectables are widely used in Latin America and China. They consist of an estrogen and a progestin combined. They are highly effective, but questions about the safety of the products sold in Latin America have not been resolved, and the formulation used in China has not been thoroughly studied. The World Health Organization (WHO) is currently supporting research on two new monthly injectables. They appear to be effective and safe and may become available as early as 1988.

Estrogen-progestin combinations injected monthly have certain advantages over 2- or 3-month progestin-only injectables (96). They produce regular bleeding episodes each month and cause less spotting and other bleeding irregularities. Also, they are less likely to cause amenorrhea, which women may fear is a sign of pregnancy. Many women in a Mexican study said that they preferred monthly injectables because the monthly bleeding reminded them to return for another injection. They thought that remembering the date of their last injection over a 2- or 3-month period would be too difficult (64). Also, if women experience side effects and want to discontinue use, the side effects of monthly preparations generally subside more quickly than those of longer-acting injectables (222, 243). In Latin America pharmacists may promote monthly injectables because they can give the injections every month. Also, women may be able to pay for a monthly injection more easily than saving for a more expensive longer-acting injection.

Monthly injectables have certain disadvantages as well. These include the inconvenience of more frequent injections, the higher total cost of 12 rather than 4 or 6 injections per year, and possible side effects of the estrogen component in some preparations (222, 296).

Two Preparations Now Available

Two estrogen-progestin formulations are currently in use:

(1) a combination of 75–150 mg **dihydroxyprogesterone acetophenide** and 5–10 mg **estradiol enanthate**, used primarily in Latin America, and

(2) a combination of 250 mg **17-hydroxyprogesterone caproate** and 5 mg **estradiol valerate**, used only in China.

The first preparation is now used by an estimated 300,000 women in Mexico and perhaps as many more in other Latin American countries. The preparation was originally developed by Squibb Pharmaceutical Corporation, which called it Deladroxate. Squibb no longer manufactures Deladroxate. The similar preparations currently marketed are manufactured by several small companies in Latin America and sold under various brand names including Perlutal and Agurin (80, 98, 204) (see photo, p. K-76). In the US, Squibb Pharmaceutical Company withdrew Deladroxate from clinical testing in the late 1960s because of concerns over (1) breast tumors in beagle dogs, (2) pituitary hyperplasia in rats, and (3) possible accumulation of estradiol enanthate in the body with continued use (89, 98, 243). Subsequently, however, questions have been raised about whether such animal findings are applicable to humans. Research suggests that the adverse effects of Deladroxate on animals may occur only with doses higher than the equivalent of a contraceptive dose (2, 62, 82, 121, 272).

In clinical tests of 150 mg dihydroxyprogesterone acetophenide and 10 mg estradiol enanthate involving nearly 23,000 cycles in 2,400 women, no pregnancies were reported. Between 8 and 26 percent of women stopped using this injectable because of bleeding problems (29, 80). Return of ovulation may be delayed slightly (131). Little

Table 8. Characteristics and Status of Monthly Injectables as of March 1987

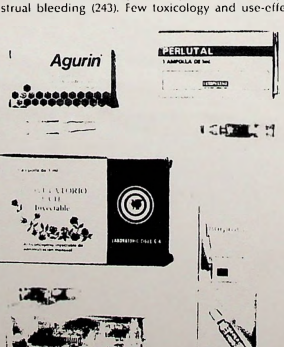
Hormone	Development & Testing	Duration of Action	Annual Trials	Phase I	Human Trials Phase II	Phase III	Estimated Availability
Cycloprovera (25 mg DMPA & 5 mg estradiol cypionate)	WHO HRP, Family Health International	1 month	Completed	Completed	Underway at 4 sites in 150 women	Underway at 12 sites in 1,200 women	First approvals expected in early 1990s
HRP102 (50 mg NET EN & 5 mg estradiol valerate)	WHO HRP, Family Health International	1 month	Completed	Completed	Underway at 4 sites in 200 women	Underway at 12 sites in 1,200 women	First approvals expected in early 1990s

WHO HRP = World Health Organization Human Reproduction Program

other research is available on any aspect of the monthly preparations currently marketed in Latin America.

Some are concerned that the synthetic estrogen in the Latin American products may build up in the body over time. This could contribute to the delay in return of fertility after discontinuation or cause unforeseen toxic effects (223, 243). Although no such effects have been reported, very little research on estrogen accumulation in women has been done. One study in four subjects found an apparent accumulation of estrogen (89). Another found no significant accumulation in six subjects (201). To avoid estrogen accumulation, half doses once a month have been tried, and some companies in Latin America sell them (204). The lower doses prevent pregnancy effectively but seriously disrupt menstrual patterns (201).

In China a formulation called Injectable Number 1 accounts for less than one percent of all contraceptive use. A woman who uses this method receives two injections the first month and one injection every month thereafter (109, 178). The major obvious disadvantage of Injectable Number 1 is that it causes very short cycles and prolonged menstrual bleeding (243). Few toxicology and use-effectiveness data on Injectable Number 1 are available, however. It is not used outside China.



Various monthly injectables consisting of a progestin and an estrogen are sold in Latin America. Little research has been done on these formulations. Two new monthly injectables, developed by WHO, may be introduced by some family planning programs through preregistration field trials in early 1988.

Two New Preparations Studied

Two other estrogen-progestin injectables provide virtually complete contraceptive protection and excellent menstrual cycle control. Both are being tested and may be marketed soon. They are:

(1) **Cycloprovera**, a combination of 25 mg depot medroxyprogesterone acetate (DMPA) and 5 mg estradiol cypionate, and

(2) **HRP102**, a combination of 50 mg norethindrone enanthate (NET EN) and 5 mg estradiol valerate (80, 98, 243).

Currently, the World Health Organization (WHO) and Family Health International (FHI) are about to complete trials of Cycloprovera and HRP102 involving about 2,400 women in three countries. Preliminary results show that both formulations are highly effective. Among women receiving Cycloprovera, only one pregnancy occurred in the first 655 woman-years of use. With HRP102, in 648 woman-years of use four women have become pregnant, but two may have been pregnant when they received their first injections (288).

In early trials both preparations have produced bleeding patterns like normal menstrual cycles (3, 71, 113, 116). Only the Philippine center has reported detailed results: most women receiving HRP102 for one year experienced unchanged bleeding patterns, while those receiving Cycloprovera tended to have somewhat shorter, less heavy bleeding each month (96). In the first nine months of the WHO/FHI multicenter trials, less than 5 percent of participants have stopped use due to bleeding irregularities, and less than 2 percent, for amenorrhea (96, 97, 288).

Side effects other than bleeding problems have been minor with both Cycloprovera and HRP102. Slight weight gain is common with both (28, 46, 80). Since both can be detected in the blood for as long as three months after an injection, there may be some delay in the return of fertility after discontinuation (28, 71, 98, 134). The only available study to date involved 18 Thai women who discontinued Cycloprovera to become pregnant. Seven became pregnant by 3 months, and 7 more by 18 months (80, 135).

Cycloprovera and HRP102 are not currently marketed. Several national family planning programs are planning preregistration field trials beginning in early 1988 (97). Along with the microspheres, microcapsules, and new long-acting esters, these new monthly injectables will comprise a new generation of injectable contraceptives.

USE OF INJECTABLES

Injectables are currently the only widely used long-acting hormonal contraceptive. An estimated 6.5 million women are using them. About five million of these women use the longer-acting injectables, DMPA or NET EN, and the remaining 1.5 million—mostly in Latin America and China—use various monthly injectables (97, 109, 212). According to surveys (see Table 9) and production and sales data, injectables are most widely used in Jamaica, Thailand, Indonesia, Mexico, New Zealand, and China.

DMPA, marketed as Depo-Provera by the Upjohn Company, is the most widely used injectable. It is approved as a contraceptive in more than 90 countries and has been used in some for as long as 20 years (246). Sales of Depo-Provera have increased steadily in recent years, from about 2 million doses in 1982—enough to protect 1.1 million women for a year—to about 16.5 million doses in 1986—enough to protect more than 3 million women (see Table 10). Limited quantities of DMPA are produced by a number of manufacturers apart from Upjohn.

NET EN, marketed by Schering AG as Noristerat, also is widely used. It is approved in more than 40 countries. Schering AG reports that sales have been increasing rapidly. The company sold about one million doses in 1981 but in 1986 sold almost five million—enough to protect 800,000 women for a year (69) (see Table 10).

The overall estimate of 6.5 million users is based on family planning survey data, program statistics, donor agency shipments, and manufacturers' sales. A precise estimate is impossible because: (1) representative sample surveys do

Table 9. Percentage of Married Women of Reproductive Age Using Injectable Contraceptives, as Reported in Representative Sample Surveys, 1974–1984

Region & Country	Year	% Using Any Method	% Using Injectables	% of Contraceptors Using Injectables
AFRICA				
Botswana	1984	29	1	4
Burkina Faso	1986	13	<0.5	2
Kenya	1977–78	7	1	9
	1984	17	1	3
Lesotho	1977	5	<0.5	1
Nigeria	1981–82	5	<0.5	2
Sudan (north)	1978–79	5	<0.5	3
Zaire (urban)	1982–84			
Kananga		12	<0.5	3
Kinshasa		36	1	3
Kisangani		19	<0.5	2
Lubumbashi		36	1	2
Zimbabwe	1984	40	1	2
ASIA & PACIFIC				
Bangladesh	1979–80	9	<0.5	1
Fiji	1974	42	<0.5	1
Hong Kong	1982	72	3	4
Indonesia (Java & Bali)	1976	28	0.5	1
Indonesia (urban)	1983			
Jakarta		44	7	17
Medan		36	5	13
Semarang		54	13	24
Surabaya		46	4	8
Ujung		33	5	15
Korea, Rep. of	1974	37	<0.5	1
	1979	54	<0.5	<0.5
Malaysia (peninsular)	1974	35	*<0.5	1
Nepal	1981	7	<0.5	1
Philippines	1978	39	<0.5	<0.5
Sri Lanka	1975	34	<0.5	1
	1982	57	2	3
Thailand	1975	36	2	6
	1978	52	5	9
	1981	59	7	12
	1984	65	8	12
MIDDLE EAST & NORTH AFRICA				
Egypt	1980	25	<0.5	<0.5
Jordan	1976	26	<0.5	2
	1983	26	<0.5	<0.5
Morocco	1979–80	20	<0.5	<0.5
Syria	1978	20	<0.5	2
Tunisia	1978	12	<0.5	1
	1983	42	<0.5	1
Yemen Arab Rep.	1979	1	<0.5	4
LATIN AMERICA & CARIBBEAN				
Barbados	1980–81	47	3	5
Bolivia	1983	26	<0.5	2
Brazil				
Amazonas (urban)	1982	54	<0.5	<0.5
Northeast region	1980	37	<0.5	<0.5
Sao Paulo	1978	66	<0.5	<0.5
Southern region	1981	66	<0.5	<0.5
Colombia	1976	45	<0.5	1
	1978	48	1	3
	1980	51	1	3
	1986	63	2	4
Costa Rica	1976	67	2	3
	1978	65	2	3
	1981	66	2	3
Dominican Republic	1975	33	<0.5	<0.5
	1983	47	<0.5	<0.5
Ecuador	1979	15	1	3
El Salvador	1978	34	<0.5	1
Guatemala	1978	18	1	6
	1983	25	<0.5	1
Guyana	1975	35	<0.5	1
Haiti	1983	7	<0.5	2
Honduras	1981	27	<0.5	1
Jamaica	1975–76	40	7	17
	1983	52	8	15
Mexico	1976–77	12	2	6
	1978	42	3	7
	1979	40	3	7
	1982	48	5	11
Panama	1976	55	1	1
	1979–80	62	1	2
Paraguay	1977	31	1	2
	1979	39	2	5
Peru	1977–78	33	1	3
	1981	43	2	4
Trinidad & Tobago	1977	55	1	2
Venezuela	1977	49	<0.5	<0.5

Source: London et al. (153), except Burkina Faso 1986: Burkina Faso (282); Kenya 1984: Kenya Central Bureau of Statistics (291); Colombia 1986 and Mexico 1982: Ochoa (294); and Thailand 1984: Chamratrithirong et al. (39)

Table 10. Worldwide Sales of Depo Provera 150 (DMPA) and Noristerat (NET EN), 1975–86

Year	Thousands of Doses Sold	
	Depo-Provera	Noristerat
1975	4,486	2
1976	4,079	28
1977	4,766	78
1978	7,041	545
1979	6,880	796
1980	7,028	557
1981	6,788	1,035
1982	7,362	1,418
1983	10,066	1,441
1984	15,628	2,485
1985	14,527	4,100
1986	16,500*	4,800*

*Estimated

Source: Schering AG (69, 213); Upjohn International (33, 58)

not cover all countries, and most surveys are now at least several years old; (2) program statistics on new clients are a poor indicator of prevalence, since discontinuation rates are not reported; (3) donor agency shipments and sales by manufacturers do not reliably indicate current use because large shipments are typically delivered in one year and used over the course of two or three years.

Among countries with surveys of contraceptive use (see **Population Reports**, *Fertility and Family Planning Surveys: An Update*, M-8, September-October 1985), **Jamaica** has the highest percentage of women using injectables. In 1983, 8 percent of married women of reproductive age, or 15 percent of all contraceptors, used DMPA. One-third of married women of reproductive age had used injectables at some time (212). There is some evidence that usage may have been higher previously. Family planning clinic records indicate that the percentage of new clients choosing injectables fell from 34 percent in 1976 (17) to 27 percent in 1983 (212). Also, a 1984 Pan American Health Organization study found overstocks of injectables in many clinics (248).

In **Thailand** DMPA has been available for more than 20 years. The government family planning program has offered DMPA since 1979 and NET EN since 1984 (212). According to the 1984 Contraceptive Prevalence Survey, injectables were the third most widely used method, after oral contraceptives and voluntary female sterilization. Between 1981 and 1984 the percentage of married women of reproductive age using injectables changed little, rising from 7.1 to 7.6 percent. In both years about 12 percent of contraceptors used injectables (39). In 1984 well over 400,000 women were estimated to be continuing users, and in 1985, 26 percent of new clients in the national family planning programs chose injectables, mostly DMPA (133, 212).

Injectables are widely used in **Indonesia**, even though the government has promoted IUDs and oral contraceptives rather than injectables (117). In 1983 in one Indonesian city, Semarang, 13 percent of married women of reproductive age—almost one-fourth of all contraceptors—used injectables. Nationally, as many as 10 percent of contraceptors used them. DMPA was introduced in 1967, but the government family planning program did not distribute it until 1978. NET EN also is available, but its use has been restricted to specific areas to prevent confusion with DMPA, since NET EN does not last as long as DMPA (212). Norplant implants have been available through the national family planning program since 1986, and use is growing rapidly (see p. K-61).

In **Mexico** about 5 percent of married women of reproductive age, or 11 percent of contraceptors, use injectables, according to a 1982 national survey. Various monthly injectables account for about 80 percent of injectables sold. Both DMPA and NET EN are available, with NET EN more popular. Controversy over DMPA has suppressed sales. Most women obtain injections at pharmacies (204). The demand for injectables is higher in rural than in urban areas (204, 212, 294).

In **New Zealand** an estimated 4 percent of married women of reproductive age use DMPA. This may be the highest level of use in any developed country. Depo-Provera has been used in New Zealand for almost 20 years. Sales increased steadily from the late 1960s to 1982, when about 86,000 doses were sold. Perhaps partly due to a highly publicized controversy over whether the injectable causes serious side effects, sales fell to about 80,000 doses in 1983. In 1986, however, sales had again neared 86,000 doses (110, 207).

In **China** production figures suggest that just under one percent of married women of reproductive age, or slightly more than one percent of contraceptors, use the monthly Injectable Number 1, which is manufactured by the government. A variety of other monthly preparations are in clinical trials (109, 274). The one million Chinese women estimated to be using monthly injectables account for about one-sixth of all women using injectables worldwide. There have been reports that use of Injectable Number 1 has been declining recently (97).

Donor Agency Supplies of Injectables

The United Nations Fund for Population Activities (UNFPA) and the International Planned Parenthood Federation (IPPF) are the major international donors of injectable contraceptives. Between 1983 and 1986 they supplied about 5.1 million doses of DMPA—enough to protect 320,000 women each year—and 1.5 million doses of NET EN—enough to protect 60,000 women each year.

DMPA accounted for about 90 percent of the injectables provided by IPPF and 70 percent of those provided by UNFPA, and NET EN accounted for the remainder. Of DMPA, over half of IPPF supplies and almost 40 percent of UNFPA supplies went to countries in sub-Saharan Africa. Three countries—Nigeria, Zaire, and Kenya—received almost one-fourth of the DMPA shipped by the two agencies. About 40 percent of all IPPF supplies and half of UNFPA supplies went to Asian and Pacific countries, mainly to Bangladesh and Nepal. Only about 9 percent of IPPF supplies and 10 percent of UNFPA supplies went to Latin American or Caribbean countries, mainly to Jamaica (123, 245).

Donor shipments of NET EN are smaller. UNFPA shipped over one million doses, but only to eight countries. Over 95 percent went to Pakistan and Bangladesh (245). IPPF supplied 32 countries but shipped less than a quarter of a million doses, three-quarters of it to sub-Saharan Africa and over half to Nigeria, Rwanda, and Zaire. The rest went mostly to El Salvador and Mexico (123).

INTRODUCING A NEW CONTRACEPTIVE METHOD

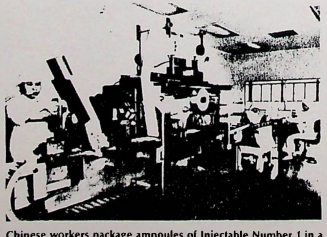
Laboratory and clinical research to test the effectiveness and safety of several new implants and injectables will be completed by the late 1980s and 1990s. But introducing a new method to the public raises other issues. Without careful preparation, the new contraceptives may be ignored by health professionals and women; unwanted pregnancies may occur; and complication and discontinuation rates may be high. To launch any new method successfully, developers, manufacturers, and program managers must carefully consider:

- manufacture and marketing,
- costs and pricing strategies,
- delivery systems,
- training of health personnel,
- communication to providers and potential users, and
- postmarketing surveillance.

Careful introduction of a new method on a worldwide basis can require the skills of various organizations as well as those of individual scientists and service providers in many countries. For example, to assist with the development and introduction of Norplant, the Population Council has worked closely with the International Committee for Contraception Research, a group of scientists organized by the Population Council; Family Health International (FHI); the Program for Appropriate Technology in Health/Program for the Introduction and Adaptation of Contraceptive Technology (PATH/PIACT); the Association for Voluntary Surgical Contraception; the World Health Organization (WHO); and the International Planned Parenthood Federation (IPPF).

Manufacture and Marketing

Because of the shift in contraceptive research and development away from private commercial firms to government agencies and nonprofit organizations (see box, p. K-70), the process of manufacturing and marketing contraceptives is changing. At present, governments, international agencies, and private nonprofit organizations, such as the US National Institute of Child Health and Human Development (US NICHD), WHO, the Population Council, and FHI have taken the lead in developing new long-acting methods. Such organizations do not manufacture and distribute contraceptives themselves, however. Thus arrangements must be made with commercial firms for large-scale manufacture and marketing. For example, to produce both the 6-capsule and 2-rod Norplant systems, the Population Council has granted an exclusive license to Leiras Medica/Huhtamaki Oy, an international pharmaceutical firm based in Finland. The agreement requires that Leiras charge a lower price to public-sector organizations and government programs than to commercial distributors (287).



Chinese workers package ampoules of Injectable Number 1 in a new factory in Shanghai. The factory currently produces injectable contraception for an estimated one million women a year. (Courtesy of PATH/PIACT)

Names for Norplant

How do you translate "Norplant"? It is not easy. The Population Council coined the name by combining parts of the words "norgestrel" (the former name for levonorgestrel) and "implant." But women around the world have chosen their own names for the method.

Some names reflect the implants' appearance or placement. In Ecuador Norplant is called *el abanico* ("the fan") because the implants are inserted in a fan-like pattern in the arm. Other names are *la mariposa* ("butterfly"), *los tubitos* ("little tubes"), and sometimes *la capsula* ("the capsule"). In Sri Lanka women call Norplant *tampatah* ("down under"), because the implants are inserted under the skin, or "sticks" (195).

In Indonesia Norplant gets the name *susuk* from the gold or other metal traditionally implanted under the skin to bestow supernatural power on the user (5, 195). Since Norplant is so widely known as *susuk*, this name is now used in pamphlets, posters, and other educational materials (see photo, p. K-59).

It is not certain who will manufacture and market the other new methods. Many of the new long-acting hormonal methods are being developed initially by nonprofit organizations. Private pharmaceutical companies in the US and Europe have the first option to market some of the new long-acting methods such as Capronor, some injectable microspheres, and some long-acting injectables and own all rights to other injectable microspheres and capsules. Given concerns about product liability, however, particularly in the US, drug companies may be unwilling to market any new contraceptives even though tests prove them to be safe and effective.

Local production of contraceptives in developing countries is an alternative to international distribution by pharmaceutical firms. In China a factory built with support from the United Nations Fund for Population Activities (UNFPA) and technical assistance from PATH/PIACT is designed to produce about 30 million doses of Injectable Number 1 each year (109). DMPA and several monthly injectables are manufactured or packaged in a number of Asian and Latin American countries (150). Local production may be possible for some of the other new long-acting methods once the manufacturing processes are established.

In most countries new methods must comply with national regulatory requirements before they can be registered and marketed. Some governments require clinical trials in-country. As part of the agreement with the Population Council, Tetras Medical takes responsibility for registering Norplant. To date seven countries—Finland, Sweden, Indonesia, Thailand, Ecuador, the Dominican Republic, and Colombia—have registered the 6-capsule Norplant system, and one country—Finland—has registered the 2-rod Norplant-2 (85, 189). Applications for approval of the 6-capsule system have been filed in other countries in Africa, Europe, Asia, and Latin America (124). An application for Norplant-2 will be filed in the US in 1987 (85).

Cost

What do the new methods cost? While prices vary depending on quantity, timing of purchase, delivery schedule, exchange rate, and other factors, the implants and injectables are generally more expensive than oral contraceptives. Shown below are sample or expected prices charged by manufacturers to donor agencies that buy in large quantities:

Sample or Expected Prices to Donors for Various Contraceptive Methods

Method	Current or Expected Price to Donors (in US$)	
	Per Dose	Per Year
Combined estrogen-progestin oral contraceptives	$ 0.15 per cycle*	$ 1.95
Norplant (5-year, 6-capsule system)	14.00	2.80
Norplant-2 (3-year, 2-rod system)	9.00	3.00
DMPA (3-month injectable)	1.00	4.00
NET EN (2-month injectable)	1.00	6.00
Cycloprovera (monthly injectable)	.80	9.60
HRP102 (monthly injectable)	.80	9.60

*Price paid by US Agency for International Development for oral contraceptives shipped to national family planning programs, as of April 1987

Sources: Blackburn (281), Castle (36), Chatwal (40), Hall (97)

Prices are not necessarily the same for all purchasers and are often lower for public or nonprofit organizations than for commercial distributors.

Norplant-2, the 2-rod system, is less expensive than the 6-capsule system, partly because the manufacturing process is almost completely automated. The cost of Norplant-2 will almost certainly be even lower as more devices are made (124). The trocar used with both systems costs about $6 (85).

The prices of other new methods are not yet established. Biodegradable pellets probably will cost less than implants or injectables because they are easier to make (79).

The cost of supplies is only part of the cost of delivering a contraceptive. Numbers of staff, staff training, and staff time per client are all important to total cost. On one hand, short-acting methods such as monthly injectables require more clinic visits than longer-acting methods. On the other hand, training health workers to deliver the longest-acting methods—inserting and removing Norplant implants or IUDs and performing sterilization—is more costly than teaching someone to administer injections. Also, these methods require relatively time-consuming procedures. In addition, implants and sterilization require minor surgical supplies: surgical gloves, sterile drapes, local anesthesia, and surgical instruments.

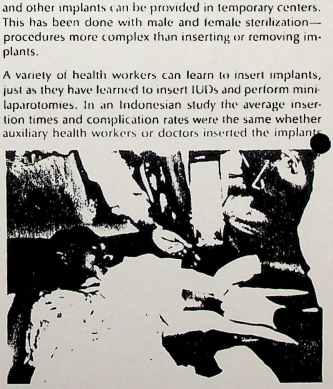
Delivery in Family Planning Programs

All of the new implants and injectables are likely to be distributed largely through family planning programs, at least initially. What is the best way to introduce a new contraceptive into a family planning program? Experience with IUDs, oral contraceptives, and now Norplant suggests that pilot studies, a specific marketing or distribution plan, and thorough training of health workers can improve the way a method is accepted and how effectively and safely it is used.

Introducing a new method on a limited basis—first in one center or one district—is a good way to assess potential demand for the product and to determine how to train health workers and counsel users (277). The Population Council has supported such pre-introduction trials for Norplant in 26 countries in Latin America, Asia, and Africa (183). WHO has sponsored similar trials to introduce NET EN and DMPA into family planning programs in six countries and is planning similar trials for Cycloprovera and HRP102 (57, 130, 199, 251).

The more channels by which a contraceptive method is distributed, the more people will have access to it. Should the new implants and injectables be offered only in clinics by doctors and other specially trained health workers? Or can they be distributed through channels that are more accessible to the community—community-based distribution, social marketing, or commercial sales? To date, Norplant has been offered only in clinics and hospitals, as recommended by the Population Council, WHO, and IPPF (119, 269). As more health workers are trained, and experience with the method grows, it is possible that Norplant and other implants can be provided in temporary centers. This has been done with male and female sterilization—procedures more complex than inserting or removing implants.

A variety of health workers can learn to insert implants, just as they have learned to insert IUDs and perform mini-laparotomies. In an Indonesian study the average insertion times and complication rates were the same whether auxiliary health workers or doctors inserted the implants.



With light from a battery-powered lamp, a doctor inserts Norplant in a woman's arm in a rural clinic in Kenya. This pilot program is assessing the training and equipment needed to deliver Norplant in clinics without electricity or running water. (Population Council)

(5, 6). In Chile, Brazil, and the US, nurse-midwives and nurse practitioners have inserted implants (52, 67). Because special training and frequent practice are necessary, however, it is unlikely that Norplant could be offered by many pharmacists or other commercial providers.

By comparison with inserting implants, giving injections is easy. Many people can learn to administer them. Around the world paramedical workers, pharmacists, and community-based workers give injections of many different medications, including contraceptives. For years mobile teams in rural Thailand have administered DMPA without difficulty (150). Community workers in rural village dispensaries have administered injectables in Haiti and Jamaica (241, 248). In Matlab and other areas of Bangladesh, injectables have been provided through community-based distribution projects (9, 108). In Mexico and Egypt social marketing programs sell monthly and 3-month injectables in retail outlets (225). No doubt the new injectables and injected microspheres can be delivered through the same channels.

To offer injectables or implants, programs need to meet the following requirements:

- Thorough training for workers (see below);
- Sufficient staff, particularly in community-based programs, to ensure that field workers can visit women on schedule;
- An accurate and simple record-keeping system to keep track of schedules;
- Medical back-up for heavy bleeding, a rare but potentially serious side effect;
- Sufficient supplies of contraceptives and other necessary equipment—including syringes, disinfectant, and autoclaves—from one source. In a pilot program in Haiti lack of DMPA accounted for 6 percent of discontinuations (241). In a community-based program in Abhoynagar, Bangladesh, field workers had to collect equipment from several different sources and so were often unable to give injections on schedule (108).
- With a long-acting implant, such as Norplant, planning to assure that women can have the implants removed any time they want and a system to notify women when the implants should be replaced.

Training

Training all health workers is essential to introducing a new method. For any of the implants and injectables, training must cover:

- The manual skills needed to deliver services, such as administering injections or inserting and removing implants;
- Sterile technique, which is essential for all implants and injectables;
- All characteristics of the method—indications, contraindications, side effects, effectiveness, and duration of action—so that health workers can help clients make informed choices;
- Risks and benefits of the method compared with other family planning methods available;
- Counseling techniques;
- Management of complications, especially heavy bleeding;
- Care of equipment and storage of supplies (in a clean, dry place; refrigeration is not needed);
- Follow-up of clients;
- Record-keeping (14, 126).

Certain training requirements are specific to Norplant implants. A model training curriculum now being developed requires each trainee to perform five insertions and five removals (166). Adequate practice in removals may be hard to obtain. Where Norplant is just being introduced, trainers often will not be able to practice removals immediately (190). PATH/PIACT has developed an artificial arm for

What Women Want to Know About Norplant

What are women's major concerns about Norplant implants? The Program for Appropriate Technology in Health/Program for the Introduction and Adaptation of Contraceptive Technology (PATH/PIACT) asked new users in the Dominican Republic, Ecuador, Indonesia, Kenya, the Philippines, Sri Lanka, and Thailand. Not surprisingly, the women had many questions, such as:

- Does insertion hurt? How long will it take?
- After the implants are inserted, will they move around in the body?
- Will people be able to see the implants?
- Will they look ugly?
- Do the incisions for insertion and removal leave scars?
- Will the implants be uncomfortable?
- Will the implants break if they are touched or bumped?
- Will the implants make it hard to move the arm?
- Can users still work? Will the implants cause weakness? (184, 274)

During counseling health workers should address these concerns as well as describe effectiveness and possible side effects. Women need to know that they will receive a local anesthetic for insertion and removal and that neither procedure is painful. Insertion takes 5 to 10 minutes. Removal takes a little longer—usually no more than 20 or 25 minutes. The implants are inserted just under the skin, not in a vein, as some women mistakenly thought. The incisions for insertion and removal leave little if any scar. If possible, during counseling a woman should have a chance to hold implants in her own hand so she can see that they are soft and flexible. Once inserted, the implants will not move, do not cause any pain, and will not break even if they are bumped or if a woman carries her child in her arms. After insertion, a woman can do any kind of work that she did before. Neither Norplant nor any other hormonal contraceptive weakens a user or her husband.

The implants are sometimes visible under the skin. Usually they look like a vein but without color (184). Few users are troubled by this. In an early clinical trial, when implants were routinely inserted in the lower arm, about 40 percent of acceptors reported that family members or friends had noticed the implants. Even so, only 7 percent of users considered the appearance of the implants to be the feature that they most disliked (237). Now implants are often placed in the inner side of the upper arm and so are less visible.

teaching insertion, but a device for teaching removals is still being developed (250).

Practice with removals is important (see box, p. K-62). A practitioner who has not had hands on experience may have problems or may be reluctant to remove implants, especially if the woman has not used them for a full three or five years (186). Even if doctors perform removals during training, when Norplant is being introduced they may not perform another for several years. Thus periodic refresher courses are needed.

There are several ways to ensure that health workers are trained in removal so that women can have their implants removed on request. One approach is to teach practitioners in two stages. In Sweden training started just after Norplant was approved, in 1985, and covered only insertion technique. A second segment of training will teach removal techniques when women want to stop using Norplant (190). Another approach is to train just a few practitioners in removal at first and refer all removals to them. In Indonesia central removal centers have been set up (165). Practitioners also can be trained at these centers.

The Population Council has established four international training centers—in the Dominican Republic, Indonesia, Chile, and Egypt. In 1985 and 1986, 28 doctors from eight countries were trained at the Dominican Republic center; at the Indonesian center 13 doctors from India, 4 from China, and 10 from five other Asian countries were trained; and 4 from Africa were trained in Finland (183, 187, 250). In Thailand, where Norplant was approved in 1986, the Ministry of Health has set up 17 training centers. About 700 doctors were trained by early 1987 (183). The model training curriculum, developed by the Association for Voluntary Surgical Contraception, the Population Council, PATH/PIACT, and Family Health International, calls for a 5-day program (14). Plans are being made to test the curriculum in several countries (125).

Sterile technique has always been important with IUDs, injectables, and sterilization. Now the risk of transmitting the virus that causes AIDS—acquired immune deficiency syndrome—makes it essential. Worldwide, more than 45,000 cases of AIDS have been reported as of March 1987 (299), and neither a vaccine nor a cure has been found. The human immunodeficiency virus (HIV), which causes AIDS, is transmitted sexually and also in blood. A number of researchers have suggested that, if contaminated needles are used in health clinics, they could transmit HIV (35, 156, 157, 175, 179, 298) (see **Population Reports**, *AIDS—A Public Health Crisis*, L-6, July-August 1986). There is no evidence yet that this has taken place. Many other serious illnesses, including hepatitis B, also are transmitted by contaminated needles. Maintaining sterile technique can be difficult when syringes, other instruments, and the equipment to disinfect them are in short supply. Even under these circumstances, however, health workers should never risk infecting their clients by using unsterilized instruments. (For instructions on disinfecting instruments, see box, p. K-63.)

Information and Counseling

In addition to health workers, other key audiences need education and information:

- Family planning program and donor agency administrators, government officials, and policy-makers who allocate funds and establish programs.
- Potential users, who need to know the risks and benefits of various methods before they can make an informed choice. Also, counseling on possible side effects can ease women's concerns, increase their satisfaction with the method, and reduce discontinuation rates (234).
- Journalists, broadcasters, and other communication media personnel, whose words and opinions reach many people.

In Sri Lanka a focus group discusses Norplant. Information from sessions like this was used to develop booklets explaining Norplant to users and potential users. (Courtesy of PATH/PIACT)

Informing the public about new contraceptive methods should begin as soon as the products are ready for widespread testing. Communication programs should continue after products are approved to keep potential users well informed, to combat any rumors that may arise, and to ensure that current users will return when they should.

For Norplant, the Population Council, PATH/PIACT, and Leiras Medica have developed special information materials. The material for administrators and health workers includes comprehensive information packets reporting scientific data; training guides on insertion and removal; and a newsletter, *Norplant Worldwide*, that describes the latest research and program experience (85, 144, 180, 194). In addition, Population Council experts and Norplant researchers meet with family planning officials and make presentations at scientific meetings.

For potential users PATH/PIACT and the Population Council have developed information pamphlets in local languages and adapted to local audiences in Ecuador, Indonesia, the Philippines, and Sri Lanka (see photos, pp. K-59, 83). A Spanish-language version for Latin America has been completed, and an African version in English and Swahili is being prepared (185). The pamphlets are meant to be used during counseling to reinforce the information given to clients (185).

Thorough and sympathetic counseling is important for all methods, old and new. During counseling sessions, health workers and clients should consider several issues—the woman's age and health, whether she and her husband want more children, how easily she can come back to the clinic for supplies, and the availability of supplies for temporary methods. For some couples, one of the new long-acting methods may offer distinct advantages; for others, established methods such as oral contraceptives or con-

doms may be preferable. As a long-acting method, Norplant is especially appropriate for women who do not want any more children but do not want to be sterilized or cannot obtain voluntary sterilization as well as for women who want a long interval between births. Also, since Norplant contains no estrogen, it is less likely to cause some of the side effects that occur with combined estrogen-progestin oral contraceptives. Thus Norplant may be preferable to oral contraceptives for women over age 35, for whom estrogen contributes to an increased risk of cardiovascular side effects. The injectables, injectable microspheres, and shorter-acting implants may be best suited for women who are spacing their children and also have convenient access to clinics or pharmacies. None of the new methods has been thoroughly tested in lactating women. Studies of DMPA, NET EN, and Norplant, however, suggest that the progestin-only methods have no harmful effects on breast milk composition or production or on the breast-feeding infant (see pp. K-63, 73).

If a woman chooses Norplant, counselors must make sure she knows that:

- She can return to the clinic or center to discuss any problems and concerns;
- She can have the implants removed whenever she wishes, for any reason whatsoever;
- Irregular bleeding is common with Norplant; however, in many women irregular bleeding diminishes with time;
- In the rare instance that pregnancy occurs, the implants should be removed immediately.
- In addition to suspected pregnancy, she should return immediately if she has severe abdominal pain, heavy vaginal bleeding, arm pain, pus or bleeding at the insertion site, repeated severe headaches, or blurred vision.
- The 6-capsule Norplant system is effective for five years and then should be removed; preliminary trials show that the 2-rod Norplant-2 system is effective for at least three years.

About half of Norplant users keep the capsules for five years. What is the best way to remind them when the capsules need to be replaced? Several approaches are being discussed. One possibility is to contact users by telephone, mail, or personal visit. This is not always feasible, however, and in large programs it would be very expensive and time-consuming. Another approach, sometimes used with IUD users, is to give each woman a card printed with the date for removal. The cards could be color-coded by the year that the implants were inserted. Three or five years later messages could be posted in clinics and broadcast over radio and television advising women who have cards of a specified color to come to the clinic to have the implants replaced (193).

Postmarketing Surveillance

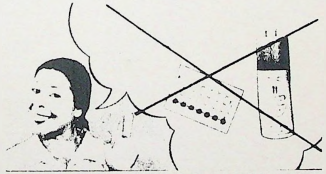
Experience with oral contraceptives and IUDs has shown that some side effects and some benefits of contraceptives are not discovered immediately. The animal and clinical trials required in most countries before contraceptives are introduced ensure that contraceptives are safe and effective in the short run. Only continued postmarketing surveillance of large numbers of women, however, can detect side effects that are rare or appear only after a long period.

Some of the hormones used in the new contraceptive methods—levonorgestrel and norethindrone—have been used for years in oral contraceptives. Their safety and side effects are well established. Nonetheless, as new delivery systems they may behave differently. Thus surveillance of these new methods will be needed. Other progestins, such as norgestimate, NT-145, and the new levonorgestrel esters, are being tested for the first time. Postmarketing studies are particularly important for these progestins.

Among the new contraceptives, only Norplant implants are on the market in several countries. WHO, the Population Council, and FHI are collaborating in setting up a large prospective study to look for any medium- and long-term effects of Norplant use. The study, which will be coordinated by the WHO Special Programme of Research, Development and Research Training in Human Reproduction, will involve 5,000 Norplant users and 5,000 controls from 10 to 12 sites in developing countries. The pilot phase of this study, involving some 450 Norplant users and 450 controls, will begin this year at three sites. All women will be followed for at least five years even if they stop using Norplant, and any hospitalization and health problems will be recorded. Any beneficial or adverse effects on health that might be associated with Norplant will be analyzed.

User Satisfaction

Many women like long-acting hormonal methods. They are very effective, convenient, and easy to use. With injec-



NO TIENE QUE ACORDARSE DE USAR NI TOMAR NADA

ESTA CONTENTA, NO LE DUELE, NO TRAE NADA ADENTRO

In this pamphlet from APROFE in Ecuador, a woman tells others why she is happy with Norplant: the implants do not hurt, and she does not have to bother with other contraceptives any more.

tables and implants, women can be assured of almost complete contraceptive protection without having to take a pill every day or use a barrier method with each act of intercourse.

Wherever injectables have been available, they have been popular. In many developing countries people would rather take medicines by injection than orally, perhaps because they associate injections with the antibiotics that have been so effective in controlling communicable diseases. Also, injectables afford privacy that appeals to some women. A woman can obtain injections outside the home without her husband's or family's knowing. Some women prefer monthly injectables to the less frequent DMPA and NET EN, according to a Mexican study, because the monthly bleeding is a good reminder to obtain the next injection (64).

Implants have been readily accepted in many of the countries where they have been tested. Some researchers worried at first that women would fear the insertion procedure or dislike the fact that the implants sometimes are visible under the skin (286). Initial experience with the method has obviated such fears. In Indonesia, for example, 57,000 women chose the method in the year since it was approved by the Indonesian Drug and Food Authority (85).

Changes in bleeding patterns remain the major cause of dissatisfaction with long-acting progestin methods. Amenorrhea is perhaps the most disturbing change because women cannot be sure that they are not pregnant (98, 154). Also, some women think that regular menstruation is essential to good health. Prolonged bleeding or spotting also can be disturbing, especially if social or religious customs restrict the activities of menstruating women.

The new long-acting methods now becoming available will offer women more choices at every stage in their reproductive lives. Developing good methods is only the first of many steps to making them available, however. Effective distribution, marketing, and information and service programs also are essential so that potential users really have a choice of these new methods available to them.

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WH 3.4

Vogue

HEALTH

tough choices

Decisions about birth control have grown mor complicated. Erica Frank, M.D. reports new findings on the pill and othe contraceptives

MY FRIEND, A DOCTOR IN HER LATE TWENTIES, had an abortion this fall. She was using a barrier contraceptive and had been conscientious about its use. She'd tried birth-control pills but felt lousy on them, and believed—correctly—that since she didn't see her boyfriend often, a barrier method was a good choice for her. My friend, though she was well-informed and intelligent, found herself caught up in the same unfortunate situation that about 1.5 million other American women find themselves in each year: with an abortion as her perceived best option.

It's become clear that, in 1989, there are no perfect contraceptive methods for women. To gain efficacy, a woman may have to sacrifice some safety; to avoid health risks, she may lose spontaneity.

The choices are difficult ones. Women who became sexually active using the pill in the pre-AIDS era may find it hard to reorient their thinking. In addition to the difficult contraceptive choices a woman must make now, she must also decide how to deal with the small but real risk of fatal illness from intercourse. No longer must women protect just their reproductive health; today they must also protect their lives (by picking partners carefully and insisting on condom use). Although partner choice is probably the most important health decision, condoms are requisite today if one is uncertain about a partner's HIV status. The reason is simple: the pill does *not* protect a woman against any sexually transmitted diseases, including AIDS.

The pill: new pros and cons

The pill has come a long way. It has changed from the high-dose estrogen and progestin pill of the last decade to a combination pill that uses the lowest possible doses of estrogen and progestin to maintain efficacy and prevent spotting.

When birth-control pills (such as Enovid 10) were first introduced in 1960, the progestin used was a 10 milligram dose of norethynodrel and the estrogen was 150 micrograms of mestranol. Today, however, birth-control pills contain less than a quarter of the old dosages. Current birth-control pills also use different hormones (progestins such as ethynod diacetate and norethindrone, and estrogens like ethinyl est diol). These changes—different hormones at lower d ages—have produced birth-control pills that may be l likely to cause cancer, have fewer adverse effects on ch terol levels, and produce fewer skin problems.

How safe is today's pill? According to *Contracep Technology* (Irvington Publishers, Inc. 1988), a medical t book, a nonsmoker's chance of death from taking the pill year is one in 63,000; one in 16,000 for a smoker. Com these pill risks with the death risks per year of having a b (one in 10,000), automobile driving (one in 6,000), and torcycle riding (one in 1,000).

The real advantages of the pill are its low failure rate an ability to prevent risks associated with pregnancy. Whil percent of women who use no method of birth control wi pregnant within a year, only about 1 percent of heterosexu active women who use the pill properly will become pregn

Historically, women feared using the pill because of t creased risk of blood clots, heart attacks, and strokes; bu low-dose pills have done much to decrease such cardiova lar risks. It's now clear that these rare cardiovascular ev occur primarily in older women (over thirty-five) who sm and in those with other conditions, such as obesity, blood pressure, diabetes, high cholesterol, or a history o diovascular disease. Also, warning signs such as heada visual changes, sudden shortness of breath, or severe c abdominal, or leg pain while on the pill have helped to potential problems for pill users.

The current health concerns with the pill: breast cancer cholesterol. Recent studies—featured prominently i press—suggest that pill users may be at higher risk of b cancer. Although these articles have suggested an assoc between the pill and breast cancer, the studies them have several epidemiological limitations. Some of the control pills studied were the original, high-dose pills, r low-dose ones currently prescribed; experts suggest th cer-causing potential of the high-dose pills may be gr Additionally, the reasons for the increased breast-canc

puted among experts. Some said duration of pill use mount; others cited a family history of breast cancer, set of menstruation, or bearing fewer children. It is t to note that most previous studies found no signifi- tionship between breast cancer and the pill. Further- is newly reported elevated risk was suggested in omen, a group in which breast cancer (even among) is extremely rare and for whom even the slightest risk makes scientists take note.

. Holmes, M.D., Ph.D., professor of medicine and of the Center for AIDS and Sexually Transmitted at the University of Washington in Seattle, says, hope the new studies linking breast cancer to the pill o be false. However, this represents a good opportu- omen to reexamine whether they really require the ncy rates that the pill provides. Some women may they'd rather use a method like foam and condoms, er prot[illegible]on against sexually transmitted diseases, an the possible adverse health risks associated with

Nonetheless, examination of all the evidence (the ponsible way for women and their physicians to isions) still indicates that the pill now being pre- ill probably represent, for most women, no substan- eased lifetime risk of breast cancer.

t but other cancers? Although experts continue to te data, risk of cervical, skin, and liver cancers is not markedly elevated in pill users, as was formerly

On the plus side, according to Robert Hatcher, ior author of *Contraceptive Technology*, "There is a good deal of evidence to suggest that the pill protects against both ovarian and endometrial cancers."

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According to Geoffrey P. Redmond, M.D., a Cleveland Clinic Foundation endocrinologist specializing in hormonal diseases of women and children, the pill may also have variable effects on cholesterol levels. While different brands of birth-control pills contain estrogens that

ittle in their effect on the body's cholesterol level, contain very different types and levels of progesn are responsible for lowering the "good" (HDL) l and raising the "bad" (LDL) cholesterol. This l-raising effect of progestins is one reason (in addoblems with decreased efficacy and spotting) to rogestin-only "mini-pill." Dr. Redmond believes future "birth-control pills will be selected accordr effects on cholesterol." He recommends that birth-control pills with low levels of "good" proch as those found in Demulen-1/35, Ovcon-35, and Modicon). According to Michael Kafrissen, ector of clinical reproductive research for Johnson tical Research Institute (associated with Ortho tical), new progestins that have even better effects rrently "dominate the market in Europe and may use in the United States in the next two years."

Who should use the pill? The ideal candidate is healthy, young, sexually active, monogamous, nonsmoking, and does not wish to get pregnant now but would like to be able to conceive later. According to Dr. Hatcher, nonsmoking women who have no cardiovascular risks "may continue taking the currently available low-dose estrogen and progestin pill until as late as age fifty." He also points out that a combination of estrogen and progestin quite similar to that found in birth-control pills (estrogen replacement therapy in the form of Premarin and Provera) has been shown to help protect against osteoporosis and cardiovascular disease after menopause.

Other medical problems, such as severe headaches or illnesses requiring certain medications, may interact with birth-control pills; a recent fracture requiring a cast may also make pill use inadvisable. If a woman falls into any of these categories, she may still be able to use oral contraception, but should discuss it with her doctor.

A substantial number of women (as many as a quarter of those who try using the pill) cannot tolerate the pill's side effects. Women may not feel well on the pill and may experience spotting, acne, breast tenderness, increased frequency of yeast infections, depression, fatigue, headaches, water retention, rash, hypertension, nausea, decreased sex drive, or weight gain. But these side effects do not affect all women (and can disappear if a woman switches to another pill formulation), and they may be countered by other benefits—for example, an improvement in sex drive, sexual spontaneity, menstrual regularity and predictability, as well as a decrease in acne and menstrual discomfort. Some data suggest that the pill can also help to protect against benign breast disease, heavy bleeding, iron-deficiency anemia, pelvic inflammatory disease, and ectopic pregnancy.

Barrier methods

For a woman who does not want to take the pill, other options are less than perfect. Although condoms are critical protection against sexually transmitted infections, the use of condoms only will produce a pregnancy in about 10 percent of typical couples who use the method for a year. Condoms, which are more effective as a method of contraception when used with a spermicide, usually fail because they're not used regularly. They also fail because they're not put on precoitally; they're used with petroleum jelly (which causes rubber to deteriorate); or they're reused, which makes them prone to breakage. In addition, condoms must have a one-inch sperm reservoir at the tip and must be removed immediately after orgasm. Similarly, although spermicidal foams, suppositories, creams, and jellies help to prevent sexually transmitted diseases (by killing infectious organisms), they typically fail as contraception; in couples using them for one year, about 15 percent of the time.

Methods such as the sponge, cervical cap, and diaphragm may permit more spontaneity than does the condom. These vaginal barrier methods, used with a spermicide, can be excellent birth-control options for women who have infrequent intercourse and are willing and able to use them. However, many women find them messy, uncomfortable, and inconvenient; failure rates are about 15 percent a year. It is ▶ 222

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OBSERVATIONS ON THE ANTIGENICITY AND CLINICAL EFFECTS OF A CANDIDATE ANTIPREGNANCY VACCINE: β-SUBUNIT OF HUMAN CHORIONIC GONADOTROPIN LINKED TO TETANUS TOXOID*†

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Observations on the antibody response and clinical effects of injection of purified β-subunit of human chorionic gonadotropin covalently linked to tetanus toxoid were made in 16 healthy young women who had previously undergone tubal ligation. Antibodies detectable by radioimmunoassay were found in 14 of the women. Clinical surveillance and immunologic, hematologic, and biochemical tests indicated excellent local and systemic tolerance to the antigen. No significant adverse effects on menstrual function, endocrine status, or health were found. Fertil Steril 34:328, 1980

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The concept of a vaccine against pregnancy is an attractive approach to fertility control and one which has received increasing attention in the last decade. The effectiveness of antibodies against hormones in interfering with their action has long been recognized.[1] Interference with the action of human chorionic gonadotropin (hCG) should prevent it from stimulating the corpus luteum to continue the synthesis of the amount of progesterone required for maintenance of the endometrium in a state to receive and nurture the trophoblast. Recently, Talwar and colleagues at the All India Institute of Medical Sciences have reported on laboratory, animal, and human studies with a vaccine prepared from the β-subunit of hCG.[2-17] The design of the vaccine rested on several principles. One was the use of only the β-subunit of hCG with the objective of reducing the chances that the antibodies would cross-react with other glycoprotein hormones. This possibility derives from the fact that the β-subunit of hCG is unique, whereas the α-subunit is common to luteinizing hormone (LH), follicle-stimulating hormone (FSH), and thyrotropin. Another principle was that of linking the β-subunit to a foreign protein, tetanus toxoid (TT), in the expectation that the human immunologic system would respond to the new entity as "foreign" and form antibodies to both its parts.

The initial investigations gave promise that application of these principles achieved the desired ends.[2-17] They showed that antibodies produced in monkeys and in humans in response to the vaccine were capable of neutralizing the biologic activity of hCG,[12] and that their cross-reaction with hLH or hFSH[11] appeared minimal. Studies conducted in monkeys[10-12] gave no evidence of toxic manifestations. Similarly, no evidence of toxicity or interference with normal menses was seen in four women to whom the vaccine was administered.[8]

In view of these encouraging results, clinical pharmacologic studies were undertaken in four clinics under the auspices of the International Committee for Contraception Research of The Population Council. The objectives of the trials were as follows: (1) to evaluate the magnitude, constancy, and duration of antibody response; (2) to determine whether immunization gave any evidence of toxicity or unwanted side reactions; (3) to determine whether the antibodies neutralized the biologic activity of hCG in in vitro and in vivo test systems; and (4) to examine the cross-reactions between the antibodies and other glycoprotein hormones.

MATERIALS AND METHODS

Subjects and Dosing Regimens. One clinic in each of four countries (Sweden, Finland, Chile, and Brazil) participated in the studies after having approval from institutional human experimentation committees and government regulatory agencies. Subjects were informed of the purpose of the trials, of the procedures to be used, and of the status of understanding of safety. To be eligible for enrollment in the trials, subjects had to be less than 35 years of age, have been sterilized by tubal ligation, be available for regular follow-up, have regular menses, not be currently breastfeeding, evidence normality on pelvic examination, not be sensitive to TT, have no underlying chronic or acute diagnosable disease, show no significant clinical morbidity, and not be on hormone or antibiotic therapy. Tubal ligation was included as a criterion because of lack of knowledge of contraceptive effectiveness and the desire to observe antibody response and health effects without the complication of pregnancy. Subjects are identified by code names and by clinic in Table 1.

Two different regimens of vaccination were used. One regimen, designated regimen A, was used in 12 of the 15 subjects. Preparation A involved use of vaccine precipitated with aluminum hydroxide. β-hCG antigen (80 μg) was given in each of four doses spaced 2 weeks apart. For injection, aluminum hydroxide precipitate suspended in 0.5 ml of saline was homogenized with 0.45 ml of sesame oil and 0.05 ml of Polysorbate 80. Preparation B involved adsorption of the antigen on calcium phosphate. Each injection provided 240 μg of β-hCG antigen. Two injections were given, spaced 1 month apart. For injection, the calcium phosphate precipitate was suspended in 0.5 ml of saline solution.

Physical Examinations and Laboratory Tests. Before vaccination, tests were conducted to assure that the subjects were healthy and met criteria for admission and to establish baseline levels from which changes caused by the vaccine could be judged. These tests included physical and pelvic examinations, clinical chemistry, fasting plasma cortisol, hematology, urinalysis, luteal phase plasma progesterone, plasma gonadotropins, DNA antibodies, titers for anti-hCG and anti-TT antibodies, and skin test for TT hypersensitivity.

During the 1st year after vaccination, physical examinations, clinical chemistry, hematology, and urinalysis were performed at the end of the 1st month and thereafter at 3-month intervals. After the 1st year they were done at 6-month intervals. Cortisol and DNA antibodies were determined at 6-month intervals. Blood samples for antibody assay were obtained monthly during the 1st year and thereafter at 6-month intervals.

Clinical chemistry tests run on serum samples at regular intervals, as outlined above, included glutamic pyruvic transaminase (SGPT), glutamic

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TABLE 1. *Subjects and Regimens in Clinical Pharmacology Study*

Clinic	Subjects	Vaccination regimen*
University of Uppsala	Kally, Ahlb, Larss	A
University of Helsinki	Bjork, Halla, Loob	A
University of Helsinki	Aalt, Hein, Borg	B
Consultorio de Planificacion Familiar	Reye, Pere, Valle	A
University of Bahia	Aine, ABdS, MASdS	A

*For description of regimen see text.

oxaloacetic transaminase (SGOT), total bilirubin, alkaline phosphatase, urea nitrogen, inorganic phosphorus, total protein, albumin, albumin-globulin ratio, glucose, cholesterol, calcium, and thyroxine. With a few exceptions, clinical chemistry measurements were made by Bio-Science Laboratories, Van Nuys, California. Serum samples were shipped frozen, packed in Dry Ice. In exceptional cases, the clinical chemistry measures were made in the investigator's home clinic. Urinalysis and hematology were conducted in the laboratories of the individual investigators.

Approximately 2 years after immunization of the subjects, a senior obstetrician-gynecologist (A. B.), who had not been involved in the studies, visited all clinics to interview vaccinated subjects independently to determine whether there was any symptomatology suggestive of an autoimmune state. He also determined the efficacy with which information had been transferred in informed-consent procedures. Women have returned to the clinic for observation on a regular basis since vaccination, and such follow-up is continuing (except for one subject who moved from the country). The period since vaccination has been 3.5 to 4 years.

Antibody Titration. Anti-hCG titers were measured by the ability of the sera to bind ^{125}I-hCG iodinated by a modified chloramine T method.[18] ^{125}I-hCG (250 pg), specific activity 40 to 50 μCi/μg, was incubated with 4 μl of serum in a total volume of 1 ml for 2 hours at 37° C followed by 16 hours at 4° C. Separation of bound and free radioactivity was achieved by the addition of 1 ml of 25% polyethylene glycol as described by Creighton et al.[18] Results are expressed as nanograms of hCG bound per milliliter of serum. At the end of the experimental period, samples were retitrated using a single lot of iodinated hCG; it is these titers that are reported. Further cross-check was afforded by titration of samples at both The Population Council and The All India Institute of Medical Sciences. Agreement was generally satisfactory. The results reported are those obtained at The Population Council. Anti-TT titers were measured by the passive hemagglutination procedure of Boyden.[20]

Vaccine. The vaccine used was prepared at the All India Institute of Medical Sciences by coupling the β-subunit of hCG with TT using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide reagent (ECDI) in aqueous solution. The β-subunit of hCG was of high purity (10,000 IU/mg of protein). It was further immunochemically purified by absorption on anti-ovine LH immunoadsorbent as described elsewhere.[4] TT was obtained from the Pasteur Institute (430 Lf/ml, 2,000 Lf/mg of protein *N*).

TABLE 2. *Medical Conditions and Complaints Encountered "During" and "Post-" Treatment*

Subject	Condition	Frequency*	
		During	Post-
Ahlb	Possible urinary tract infection	1/10	
	Weight gain	2/10	
Larse			
Bjork	Fluid retention	1/10	
	Breast tenderness	1/10	
	Short cycles	1/10	
	Hypoglycemic attack		1/11
	Rheumatic pain		1/11
Halls	Rash at injection site	2/8	
	Varicose vein operation		1/9
Loeb	Edema	4/10	
	Weight gain	1/10	
	Vaginitis		1/12
Aalt	Adnexa slightly enlarged	1/6	
	Slight nonvascular change	1/5	
	Influenza	1/5	
	Irregular menses (low estrogens)	1/5	
	Urinary infection		1/8
Hein	Adnexa slightly enlarged	1/12	
	Influenza	1/12	
	Uterus slightly enlarged, tender		2/12
	Uterine infection		1/12
	Bronchitis		1/12
Borg	Rash at injection site	1/7	
	Excessive menstruation	1/7	
	Slight pain in colon		1/12
	Migraine		1/12
	Mild skin infection		1/12
Reyi	Colostrum	3/14	1/8
	Dizziness and vomiting 1st day of menses	1/14	
	Herpes on lip	1/14	
	Somnolence		1/8
Pers	Colostrum	3/18	1/9
	Premenstrual abdominal pain	2/18	1/9
	Adnexal pain	1/18	
	Dysmenorrhea	1/18	2/5
	Nausea and vomiting	1/18	
	Tonsillitis	1/18	
	Trichomonas infection	1/18	
Valle	Headache	1/7	
	Influenza	1/7	
	Dyspareunia	1/7	
	Adnexal enlargement and pain		2/13
	Oligomenorrhea		1/13
Aine			
ABdS			
MASdS	Soreness at site	1/7	
	Dental abscess	1/7	
	Pelvic inflammatory disease		1/11
	Acute vaginitis		1/11
	Premenstrual spotting		1/11

*Number of times condition recorded/number of opportunities for its recording.

TABLE 3. *Clinical Chemistry Measurements of Vaccinated Subjects before Vaccination, during Response, and after Return of Antibody Titers to Baseline*

	Normal range	Before*	During*	Post-*
Total protein (gm/100 ml)	6.6–8.3	7.17 ± 0.70	7.34 ± 0.60	7.52 ± 0.40
Albumin (gm/100 ml)	3.5–5.0	4.40 ± 0.33	4.39 ± 0.40	4.33 ± 0.53
Albumin-globulin ratio	1.0–2.2	1.56 ± 0.47	1.54 ± 0.52	1.57 ± 0.57
Cholesterol (mg/100 ml)	135–316	193 ± 30	195 ± 30	206 ± 33
Glucose (mg/100 ml)	70–110	86.6 ± 14.8	83.4 ± 13.3	85.2 ± 11.9
Inorganic phosphorus (mg/100 ml)	2.5–4.8	3.69 ± 0.67	3.69 ± 0.92	3.38 ± 0.46
Calcium (mg/liter)	4.6–5.5	5.74 ± 1.99	5.31 ± 1.47	4.95 ± 1.46
Alkaline phosphatase (units)	38–148	54.9 ± 21.3	52.4 ± 18.2	57.5 ± 16.3
Uric acid (mg/100 ml)	2.8–7.5	3.78 ± 1.08	4.14 ± 1.15	4.23 ± 1.15
Urea N (mg/100 ml)	8–26	14.5 ± 4.70	14.6 ± 4.01	14.2 ± 4.85
Bilirubin (mg/100 ml)	<1.5	0.70 ± 0.39	0.65 ± 0.25	0.68 ± 0.46
SGPT (units)	6–40	20.2 ± 6.47	18.19 ± 7.04	15.5 ± 8.68
SGOT (units)	13–59	28.0 ± 7.92	23.3 ± 5.97	22.8 ± 8.21
Thyroxine (μg/100 ml)	4.6–11.2	6.48 ± 1.16	6.91 ± 1.39	7.21 ± 1.30

*Values are means ± standard deviation. See "Materials and Methods" for further definition of "during" and "post-."

To effect coupling, 8 mg of the processed β-subunit were mixed with 1000 Lf of TT and 40 mg of ECDI in 8.0 ml of 0.05 M sodium phosphate buffer (pH 7.4) in 0.9% saline, and the mixture was incubated for 6 hours at 4° C against 0.05 M sodium phosphate buffer (pH 7.4) in 0.9% saline. It was then filtered through a Millipore membrane (0.45 μm pore size) to sterilize, and 5.0 ml of sterile 10% potassium aluminum sulfate dodecahydrate solution was added. After thorough mixing, 5.0 ml of 10% sodium carbonate solution was added to precipitate aluminum hydroxide. The suspension was distributed into sterile glass vials. Preparation of the calcium phosphate-adsorbed material was similar in principle, the preparation of calcium phosphate being effected by adding sterile Na_2HPO_4 and $CaCl_2$.

Analysis of this batch of vaccine on sucrose density gradients (5% to 40%) was carried out by centrifugation at 105,000 × *g* for 16 hours and subsequent estimation of β-hCG in each fraction by radioimmunoassay. These determinants indicated that only 10% of the β-hCG was coupled to TT in this particular batch. Subsequent experience has shown that the degree of conjugation varied with the type of TT and the medium in which it was suspended.

Analysis of Results. For purposes of analysis, findings were grouped into three time intervals for each subject. They were labeled "pre-," "during," and "post-" treatment. The "during" treatment period encompassed the 200 days after the first vaccination or the period of significant hCG antibody titers, whichever was the longer. The significance of difference between values obtained during these three periods was tested by using Student's *t* distribution, comprehending all observations and taking into account the covariance of the repeated observations on the same individuals. To calculate the mean value of a set of observations during a specified time interval (e.g., "before"), the mean value for each individual was calculated first, and the mean of this value was used in the determination of the mean for all individuals. Some observations on individuals were missing.

RESULTS

Patient Observations and Complaints. Complaints voiced by subjects during the interval from

TABLE 4. *Hematologic Parameters before Vaccination, during Response, and after Return of Antibody Concentrations to Baseline*

	Normal range	Before*	During*	Post-*
Hemoglobin (gm/100 ml)		12.9 ± 0.8	12.9 ± 1.1	13.4 ± 1.8
Hematocrit (%)	37–47	39.8 ± 2.2	39.9 ± 2.6	39.6 ± 2.5
White blood cells (thousands/cu mm)	5–10	6.3 ± 1.2	6.3 ± 1.1	6.3 ± 1.8
Lymphocytes (%)	20–40	36.2 ± 7.8	36.8 ± 6.6	35.9 ± 7.8
Neutrophils (%)	40–60	58.1 ± 8.9	54.1 ± 7.1	54.6 ± 9.6
Monocytes (%)	4–8	4.81 ± 1.9	4.33 ± 1.1	5.67 ± 7.3
Basophils (%)	0–1	0.20 ± 0.4	0.55 ± 0.9	0.36 ± 0.4
Eosinophils (%)	1–3	4.16 ± 2.8	3.60 ± 2.2	4.11 ± 2.5
Sedimentation rate	<20	11.9 ± 4.3	12.2 ± 5.1	13.8 ± 7.5

*Values are means ± standard deviation. See "Materials and Methods" for further definition of "during" and "post-."

TABLE 5. *Significant Changes with Direction of Change between Earlier and Later Values Indicated by Arrows*

	Before vs. during	During vs. post-	Before vs. post-
Total protein			** ↓
Cholesterol		* ↓	** ↓
Uric acid	* ↑		** ↑
SGPT	* ↓	* ↓	* ↓
SGOT			* ↓
Monocytes		* ↑	

*Significant at $P < 0.05$.
**Significant at $P < 0.025$.

first vaccination to the present, and conditions detected by physical examination, are summarized in Table 2, together with indication of whether the event occurred "during" treatment or "post-" treatment. The number of opportunities for registration of the condition (clinic visits) is also indicated. There were two instances of rash at the injection site and another instance of some pain at the injection site. Edema and weight gain, which were interpreted by the clinician (T. L.) as being premenstrual in origin, were recorded in two subjects following vaccination. Slight adnexal enlargement in two subjects, adnexal pain in another, and adnexal enlargement and pain in a fourth were encountered. Colostrum was recorded in two subjects and breast tenderness in another. One subject had a transient episode of rheumatic joint pain.

Body weight increased an average of 0.5 kg between pretreatment and "during" treatment periods and an average of 0.5 kg between "during" and "post-." There were five losses and eight gains in the first instance, and three losses and seven gains in the second.

Clinical Chemistry and Hematology. Clinical chemistry and hematology findings "before," "during," and "post-" treatment are summarized in Tables 3 and 4. Parameters that changed sufficiently to meet tests of statistical significance are identified in Table 5. The mean values of all clinical chemistry measures fell well within the "normal" range for each parameter with the exception of serum calcium values (Table 3). The "before" treatment mean for serum calcium exceeded the "normal" limits because of exceptionally high values for the clinic in Brazil. Among the hematologic measurements, the mean eosinophil values exceeded normal limits at all times. The reason is not known. It may represent parasitic stimulation.

Plasma cortisol values were obtained "during" treatment on seven subjects. Values below the "normal" range of 5 to 20 μg/100 ml were recorded in two subjects. Subsequent values were in the normal range for one of the subjects. Later analyses have not been obtained on the second subject.

DNA antibody readings slightly above (1.2 and 1.3) the normal of under 1.0 μg of DNA bound/ml, but in a range considered nonspecific, were obtained for four subjects "during" treatment. Values have been consistently below 1.0 "post-" treatment for all except one subject for whom "post-" treatment analyses are not available.

Clinical chemistry and hematology findings were also analyzed for evidence of trends in individual subjects and for evidence of notable changes in the percentages of subjects with values falling outside the "normal" limits (as defined by the testing laboratory). Among clear-cut trends in individual subjects were a decrease in alkaline phosphatase in one subject (Halla) and an increase in another (Hein); decreases in SGPT in three subjects (Aalt, Halla, and ABdS) and increases in monocytes in one subject (Loob). Trends in the number of subjects with individual values beyond the "normal" limits were as follows: three subjects with "high" inorganic phosphorus values "during" treatment and none at other times; five subjects with hemoglobin below 12 gm/100 ml "during" treatment and only one before treatment; and four subjects with "low" SGOT and three with "low" SGPT "post-" treatment versus none before treatment.

TABLE 6. *Days of Bleeding per Episode (A) and Days between Bleeding Episodes (B)*

Subject	Before*			During*			Post-*		
	A	No.†	B	A	No.†	B	A	No.†	B
Kallg				5.1 ± 0	7	27.1 ± 1.7	5.2 ± 0.2	20	25.1 ± 0.6
Ahlb	8.7 ± 0.4	3	21.3 ± 2.5	8.1 ± 0.6	10	17.7 ± 0.5	8.3 ± 1.3	26	21.1 ± 5.7
Larsa	4.0 ± 0	2	24.0 ± 0	4.0 ± 0	7	24.6 ± 0.7	4.0 ± 0	4	27.2 ± 1.1
Bjork	2.3 ± 0.2	7	34.6 ± 6.0	3.4 ± 0.2	9	24.0 ± 1.3	3.5 ± 0.2	37	23.1 ± 1.0
Halla	3.0 ± 0	2	23.0 ± 0	4.2 ± 0.3	6	25.5 ± 3.3	2.8 ± 0.1	32	23.2 ± 0.3
Loob				5.0 ± 0.7	4	18.7 ± 0.6	4.5 ± 0.2	13	21.2 ± 0.7
Aalt	5.5 ± 0.5	2	25.0 ± 2.0	4.7 ± 0.3	3	62.0 ± 29.0	4.8 ± 0.2	32	27.0 ± 1.3
Hein				3.1 ± 0.4	8	23.1 ± 1.4	2.7 ± 0.6	15	23.0 ± 0.3
Borg	4.0 ± 0	2	22.5 ± 1.5	4.0 ± 0	7	25.5 ± 2.1	3.8 ± 0.2	28	23.0 ± 0.8
Reye				3.2 ± 0.2	9	23.0 ± 0.9	3.5 ± 0.5	4	22.2 ± 0.2
Pere	3.5 ± 0.5	2	19.5 ± 5.5	3.7 ± 0.2	7	24.3 ± 0.8	3.9 ± 0.3	7	22.6 ± 0.8
Valle	3.6 ± 0.2	4	29.2 ± 4.7	4.6 ± 0.5	7	24.6 ± 1.9	4.3 ± 0.4	7	20.9 ± 3.1
Aine	3.8 ± 0.3	4	27.5 ± 0.5	4.9 ± 0.3	12	28.2 ± 3.0	5.5 ± 0.5	2	24.0 ± 2.0
ABdS	5.0 ± 0.6	3	25.7 ± 1.2	6.1 ± 0.4	13	25.1 ± 2.8	6.8 ± 0.5	17	23.8 ± 1.8
MAdS	4.5 ± 0.3	4	25.5 ± 0.5	4.6 ± 0.2	7	25.3 ± 0.9	4.8 ± 0.4	13	25.5 ± 0.7
Average	4.3 ± 0.5		25.3 ± 1.2	4.6 ± 0.3		26.6 ± 2.6 24.0 ± 0.7‡	4.6 ± 1.5		23.5 ± 2.0

*Values are means ± standard error.
†Number of observations.
‡Excluding subject Aalt.

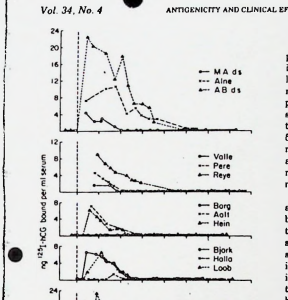

FIG. 1. Antibody responses in women vaccinated with β-hCG-TT vaccine.

All urinalysis results were normal.

Although the number of pertinent data is small, progesterone assays of plasma samples taken during the luteal phase (defined as 18 days since the last menses and 4 to 11 days prior to the next menses) gave no indication of correlation between progesterone levels and anti-hCG titer. Among 19 samples with binding capacity for ^{125}I-hCG less than 2 ng/ml, the average progesterone level was 6.8 ng/ml, and six samples had values less than 4 ng/ml; among 13 samples with binding capacities above 2 ng/ml, progesterone levels averaged 7.7 ng/ml, with three samples having levels below 4 ng/ml.

Menstrual Cycles. Menstrual cycles have been analyzed in terms of days of bleeding and days between bleeding episodes. Totaling the two gives the cycle length. Values for individual subjects are summarized in Table 6. Treatment has not caused significant effects on the number of days of bleeding and no impressive trend has been seen for any individual subject. Neither are there significant trends in the average number of days between bleeding for the group as a whole, or for individual subjects. One subject (Aalt) did show a 120-day period of amenorrhea following vaccination, from which she recovered spontaneously. She had occasionally experienced periods of amenorrhea during the previous several years.

Antibody Responses. Antibody responses in terms of anti-hCG titers are represented in Figure 1. Responses differed in both duration and intensity, with the longest duration of detectable titers being 400 days. Only one subject (Borg) failed to show a response. Responses in two other subjects (Halla, Valle) were extremely low.

All subjects showed a response in anti-TT titers. An attempt to correlate anti-hCG and anti-TT response is represented in Figure 2. It shows the areas under the anti-hCG and anti-TT curves during the first 400 days after vaccination in arbitrary units. A trend toward a greater anti-hCG response with a greater anti-TT response is evident. The greatest discrepancies from the trend lie in four subjects who evidenced a high anti-TT response and only a low anti-hCG response. There was no clear-cut correlation between previous TT vaccination and magnitude of anti-hCG response. In most cases, the anti-TT titers and the anti-hCG titers rose simultaneously. In two instances, very high anti-TT titers were attained (1:10,400), while anti-hCG titers were still at zero. hCG titers had reached 6 and 1.8 ng of ^{125}I-hCG bound/ml of serum 2 weeks later.

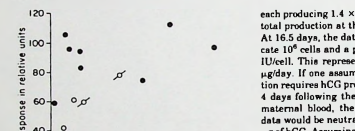

FIG. 2. Comparison of areas under anti-hCG and anti-TT response curves for subjects receiving β-hCG-TT. ●, Responses in subjects who had had previous vaccination; ○, subjects who believed they had not recieved previous TT vaccination but who had appreciable anti-TT titers before receiving β-hCG-TT vaccine.

Antisera were capable of neutralizing the activity of hCG in stimulating testosterone production in Leydig cell cultures. They showed some cross-reaction with hLH as has been detailed in an earlier publication.[17]

DISCUSSION

The findings of this study confirm the report by Kumar et al.[8] that antibodies capable of interacting with hCG can be elicited in humans by coupling the purified β-subunit with a protein that is antigenic to humans. The magnitude of the response is somewhat lower than that reported by Kumar et al.[8] This may be a result of the small percentage of the β-hCG that was actually coupled to TT in the present study. The potency of β-hCG polymer as an antigen for humans is not known but it cannot be high, as indicated by the moderate antibody response of most subjects in the present study.

The level of antibody titer required to interfere with pregnancy is unknown. Some estimate of the amount of hCG that might be produced by the developing trophoblast can be calculated from the data of Braunstein et al.[21] These investigators estimate that at 10 days after ovulation the trophoblast consists of approximately 3000 cells, each producing 1.4×10^{-2} IU of hCG/cell/day. The total production at this rate would be 4.2 μg/day. At 16.5 days, the data of Braunstein et al.[21] indicate 10^6 cells and a production rate of 7.9×10^{-4} IU/cell. This represents a total production of 79 μg/day. If one assumes that pregnancy termination requires hCG production to be neutralized for 4 days following the first appearance of hCG in maternal blood, the requirement based on this data would be neutralization of approximately 40 μg of hCG. Assuming the correctness of these estimates and assuming that only the antibodies in the serum are available for inactivation of hCG, binding capacity for 20 ng of hCG/ml of serum would be required for effectiveness.

The study has given no evidence of disturbing physiologic effects as judged either by symptoms and complaints or by clinical chemistry. The upward trend in average serum protein levels is small and reaches significance only in comparison of levels before treatment and levels after antibody titers had returned to baseline. The upward trend in uric acid serum levels is small, and no values were above the "normal" range. Some were below the normal range. The downward trends in serum transaminase values are not believed to have clinical significance. The higher frequency of "high" inorganic phosphorus values "during" treatment is difficult to interpret and there is no significant trend in mean values.

Although there were four instances of adnexal enlargement or pain, this condition occurs with appreciable frequency in untreated women, and the absence of a control group examined at equal frequency makes the finding difficult to interpret.

The one episode of rheumatic joint pain is not thought to be related to the vaccine. Upon requestioning, the subject was found to have had such episodes with fairly high frequency before administration of the vaccine.

In conclusion, the trial of the vaccine has confirmed that it elicits production in humans of antibodies capable of combining with hCG. This alone gives no assurance of effectiveness in preventing pregnancy, and the marked variation in response among subjects indicates a need to modify the vaccine before satisfactory effectiveness can be expected. Modifications will require additional safety tests. However, it is reassuring that no significant evidence of deleterious effects on the health or well-being of the subjects emerged from the present studies.

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PHASE I CLINICAL TRIALS WITH THREE FORMULATIONS OF ANTI-HUMAN CHORIONIC GONADOTROPIN VACCINE

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ABSTRACT

Comparative phase I clinical trials were carried out in 5 centres with three formulations of beta-hCG-based vaccines inducing antibodies against human chorionic gonadotropin. The objectives of these trials were to determine their relative immunogenicity, duration, reversibility and safety. A total of 116 tubal ligated women volunteers were enrolled in the study and 101 subjects were followed-up for one year or more until the antibody titres declined to near zero levels. Every woman receiving the vaccine produced anti-hCG and anti-tetanus antibodies. Clinical examination carried out at intervals of 4-6 weeks revealed no abnormality. No serious side effects or adverse reactions were reported with any of the formulations during primary immunization with three monthly injections of the vaccine. Eleven women, however, demonstrated hypersensitivity to test dose at the time of the booster injection. The reaction was to tetanus toxoid; gonadotropin subunits conjugated to another carrier did not evoke any such reaction. Progesterone in bleeds taken at mid-luteal phase, as well as complete progesterone and estradiol done in two immunized women, indicated normal ovulatory cycles. Immunization with these formulations had no significant effect on haematological, clinical chemistry and other metabolic parameters. In summary, the results indicate that none of the three beta-hCG-based contraceptive vaccines had any adverse effects clinically, on endocrine status and metabolic parameters. Formulations A and B induced comparatively higher anti-hCG titres than M. Thus, further work can be undertaken to study the efficacy of these vaccines in humans for preventing pregnancy.

INTRODUCTION

A number of contraceptive vaccines which induce the formation of antibodies against human chorionic gonadotropin (hCG) are under development. A prototype vaccine consisting of the beta-subunit of hCG linked to tetanus toxoid (TT) was found effective in generating antibodies in women against hCG, together with creation of immunoprophylaxis against tetanus (1). The antibodies were competent to bind with hCG administered exogenously and neutralize the bioactivity of the hormone in vitro and in vivo (1,2). The antibody response was reversible and phase I studies conducted in six centres in five countries showed that the vaccine was safe and devoid of side effects (3-6). However, it was noticed that there was a wide variability of antibody titres amongst the recipients and those with inadequate titres were not protected from pregnancy.

Further research was directed towards the development of formulations with improved immunogenicity. Addition of an adjuvant, sodium phthalyl lipopolysaccharide (SPLPS) in the first injection increased antibody titres. Antibodies with better bioneutralizing capacity were produced in experimental animals by using a heterospecies dimer, where beta-hCG was associated with alpha-ovine LH (7). Similarly, a mixture of beta-hCG and beta-oLH, each linked to carrier, gave a better immune response in monkeys than the subunits alone (8). It was further found that repeated injections with a given carrier such as TT did not produce high response in all animals. However, monkeys hyporesponsive to the TT-linked vaccine produced higher titres when the hormonal subunit was presented on an alternate carrier, such as cholera toxin chain B (CHB). These investigations led to the development of two new formulations for the beta-hCG vaccine besides the earlier version beta-hCG-TT (formulation B). These were: alpha-oLH-beta-hCG-TT/CHB (formulation A) and mixture of beta-hCG-TT/CHB and beta-oLH-TT/CHB (formulation M). The present study was undertaken with the objectives of determining the relative immunogenicity, reversibility and safety of these formulations in women. This communication is a report on the multi-centric clinical trials carried out on these vaccine formulations. The approval of the Institutional Ethics Committee was obtained, besides the permission of the Drug Controller of India.

MATERIALS AND METHODS

Beta-hCG purified from hCG (10000 to 13000 IU/mg) was made available by the Population Council. Ovine LH subunits were purified from crude lyophilized sheep pituitary powder (Phoenix Chemical Ltd., Christchurch, New Zealand) by following the procedure of Liu and Ward (9). The homogeneity of the subunits was checked on sodium dodecyl sulphate-polyacrylamide gel electrophoresis (SDS-PAGE), where individual subunits migrated as single diffuse bands in a 10% gel. Heterospecies dimer of beta-hCG and alpha-oLH was generated as described elsewhere (7).

Tetanus toxoid (Wyeth Laboratories, Marietta PA, Batch No. 4381, 350 Lf/ml) was purified on a Sepharose-6B column. The high molecular weight (150 kD) component was used for conjugation. The homogeneity of cholera toxin chain B (Batch CHB 10000, Institut Merieux, Lyon, France) was checked on SDS-PAGE: toxin B chain migrated as a single protein band of about 12 kD molecular weight.

Conjugates of gonadotropin with carrier were prepared by coupling beta-hCG, beta-ovine LH or heterospecies dimer with TT using a hetero-bifunctional agent, succinimidyl-4-(N-maleimidomethyl) cyclohexane-1-carboxylate, and with CHB by the periodate oxidation method as described (10).

The three vaccine formulations investigated were B, A and M. These were adsorbed on aluminium hydroxide (Alhydrogel, Batch No. 1635 Superfos, Vedbaek, Denmark) under aseptic conditions. Each ampule marked for the first injection contained one mg of detoxified lipopolysaccharide (SPLPS). Each preparation was tested for sterility and pyrogenicity before release to the clinics.

The subjects enrolled were tubectomized women of 25 to 35 years of age, of proven fertility, reporting regular menstrual periods, non-lactating with no known history of allergy, and willing to come for regular follow-up. The volunteers were enrolled after obtaining their written consent. The protocol envisaged the study on a total of 105 subjects, distributed over five collaborating centres located in 3 different parts of the country. Each formulation of the vaccine was investigated at two dose levels, i.e. 100 µg and 500 µg gonadotropin content. Thirty subjects were to be immunised with each vaccine formulation, 15 at 100 µg dose level and 15 at 500 µg dose level (3 per dose per vaccine per centre). Fifteen subjects were to receive vehicle only and serve as controls (3 per centre).

The subjects after enrollment were followed-up for 2 cycles to record the menstrual cycles and basal clinical chemistry and haematology values. Progesterone levels in blood samples taken between day 21 and 25 of cycle were also determined.

Before each injection, subjects were tested for possible sensitivity to the vaccine by injecting a test dose (0.05ml) intradermally. The vaccine in a volume of 0.8 - 1.0 ml was given intramuscularly into the gluteal muscle. Primary immunization consisted of 3 injections at an interval of 4-6 weeks; a booster injection was given at 24-32 weeks. The subjects were clinically examined at 4-6 weeks intervals or earlier if considered necessary by the subject or the investigator during the study period of one year. All the subjects were asked to maintain their menstrual diary card.

Antibody titres against hCG and other characteristics of the antibodies were determined in blood samples taken at 4- to 6-week intervals (10). Cross-reactivity with hLH was determined by a competitive inhibition assay. Anti-carrier antibody levels were determined by enzyme-linked immuno-sorbent assay. Various dilutions of each antiserum (1:200 to 1:8000) were incubated at 37°C for 1 hr with the respective antigen coated onto 96-well plate. After washing, incubation was carried out with protein A-horseradish peroxidase conjugate, colour developed with orthophenylene diamine and hydrogen peroxide, and absorbance read at 490 nm. Anti-TT and anti-CHB titres were computed from readings in linear range and expressed as units/ml serum. Haematological parameters (eg. hemoglobin, total and differential leucocyte counts, platelet count and packed cell volume) and clinical chemistry

parameters (eg. glucose, cholesterol, creatinine, bilirubin, urea, alkaline phosphatase, SGOT, SGPT) were repeated at 24 weeks and 52 weeks following immunization.

RESULTS

A total of 116 subjects were enrolled, out of which 15 dropped out from the trial (Table I). Amongst these, two subjects were excluded from the trial due to non-adherence to the study protocol, one subject had completed initial immunization schedule but was lost to follow-up at 32 weeks.

TABLE I: Subject enrollment and dropouts

Vaccine	Code	Dose(µg)	Enrollment	Dropouts
Alpha-oLH-beta-hCG	A	100	17	3
-TT/CHB		500	16	1
Beta-hCG-TT	B	100	18	4
		500	16	1
Beta-oLH-TT/CHB +	M	100	16	1
beta-hCG-TT/CHB		500	17	2
Control (Vehicle only)	C	-	16	3
Total			116	15

The remaining 12 subjects did not complete immunization schedule and discontinued the treatment due to different reasons; 4 subjects due to reactions following injections, 5 due to other medical reasons and 3 owing to personal reasons. The details of subjects discontinuing due to side effects and other medical reasons are given in Table II. In the remaining 101 subjects who completed 52 weeks or more of observation, no serious side effects were reported with any formulation.

Reactions to Primary Immunization

Out of 88 subjects who were immunized with different formulations of the hCG vaccine, 63 subjects did not have any complaints following first injection (Table III). The remaining 25 subjects (28%) had minor complaints such as erythema, pain at site of injection, fever, oedema,

TABLE II: Details of dropout cases

Formulation	Injection 1st	2nd	3rd	Booster
	Reactions			
A-100	Dizziness, palpitation and fever	No complaint	No complaint	Erythema 6. booster not given
B-100	No complaint	No complaint	Erythema 6x5cm, inj. not given	
M-500	Redness, edema, urticaria, fever	2nd injection not given		
M-500	Redness, itching, inj. not given			
	Medical reasons			
A-500	Dizziness	No complaint	No complaint	Diagnosed t have TB, booster not given
B-100	Fever, pain at site	No complaint	Did not come for inj. due to PID	
B-500	No complaint	No complaint	Edema feet, face and joint pain	Symptoms persisted, booster not given
M-100	Joint pain, swelling of interphalangeal joints of fingers and right toe	Erythema swelling (6x5x3 cm)	Inj. not given due to joint pain	
Control	No complaint	No complaint	No complaint	Chronic bronchiti booster not given

TABLE III : Reactions/complaints* following 1st injection

Formulation (Subjects)	A-100 (14)	A-500 (15)	B-100 (14)	B-500 (15)	M-100 (15)	M-500 (15)	Control (13)
No complaint	8	11	10	13	10	11	10
Erythema/ swelling at site	2	1	2	1	-	2	-
Pain at site	2	3	-	-	3	2	2
Fever	2	1	2	-	3	1	2
Generalised rash/itching	1	-	-	1	-	-	-
Leg pain	1	1	-	-	-	-	-
Nausea/ vomiting	1	-	-	-	1	-	-
Weekness/ dizziness	-	-	-	-	-	-	1

* Some subjects reported more than one complaint.

generalised rash, transient joint pain, nausea, muscle pain and giddiness. Out of 13 controls, 3 subjects (23%) also reported pain at the site of injection, fever and weakness. The number of subjects with such complaints were less following the second and third injections (Table IV).

The data was also analysed for the number of subjects who developed side effects after one, two, three or all four injections. Amongst the 49 subjects who reported side effects following injections, a majority of them (31 cases) reported complaints only once. Only one subject had complaints following all four injections.

Hypersensitivity Reaction to Booster

Out of 89 subjects who received booster dose of the vaccine, 11 subjects manifested senstivity to test dose (Table V). Hypersensitivity reaction to the test dose in ten subjects was obviated by giving the booster injections either without carrier or with alternate carrier such as CHB. This indicated that the sensitivity was to the carrier TT and not to the hormonal subunits attached to it.

TABLE IV: Reactions/complaints* following 2nd/3rd injection

Formulation (Subjects)	A-100 (14)	A-500 (15)	B-100 (14)	B-500 (15)	M-100 (15)	M-500 (15)	Control (13)
2nd injection							
No complaint	12	13	13	14	12	13	11
Erythema/ swelling at site	-	-	-	1	2	1	-
Pain at site	-	1	-	1	2	-	1
Fever	-	-	1	-	-	2	1
Joint pain	1	-	-	-	-	1	-
Muscle/ leg pain	1	1	-	-	-	-	-
Nausea/ vomiting	1	-	-	-	-	-	-
3rd injection							
No complaint	13	14	13	14	14	14	13
Pain at site	-	1	1	-	1	1	-
Fever	1	-	1	1	-	1	-

* Some subjects reported more than one complaint.

Hormonal Profile

The protocol envisaged progesterone estimation in only one blood sample taken during the luteal phase. In spite of our best efforts, the blood samples could not be collected every time during the mid-luteal phase. However, the data was analysed retrospectively in relation to the day of onset of menstruation. Table VI represents the data in women whose blood was drawn between 3 and 7 days before the onset of menstruation. The values are indicative of ovulatory cycles. It is further apparent that the progesterone values are not influenced by the prevailing anti-hCG antibodies, nor with the degree of cross-reaction with hLH. In two women, it was

TABLE V: Hypersensitivity reactions with test dose at the time of booster injection

Formulation	Complaint	Reaction due to
A-100	Reaction	TT
A-100	Reaction after 12 hours	Carrier
A-500	Reaction	TT
A-500	Reaction	Carrier
A-500	Generalized itching after 12 hours	Carrier
A-500	Pain at site	Carrier
B-500	Fever for 3 days after 24 hours	Carrier
B-500	Odema and redness at site after 12 hours, disappeared in 2 days	Carrier
M-100	Reaction	Carrier
M-100	Reaction	Carrier
M-500	Large wheal formation, itching and redness	Carrier

possible to draw blood on a voluntary basis on alternate days during the luteal phase. The profiles of estradiol and progesterone are shown in Fig. 1. These levels again indicate that the cycles were ovulatory.

Haematological and Clinical Chemistry Parameters

Haematological parameters (hemoglobin, differential and total leucocyte counts, platelet count and packed cell volume), metabolic parameters (glucose and cholesterol), hepatic function tests (bilirubin, SGOT, SGPT, alkaline phosphatase) and kidney function tests (urea and creatinine) were done before and after immunization at 24 weeks and 52 weeks. The data indicate that the pre- and post-immunization values for the above parameters were comparable and were within the normal range (Tables VII, VIII).

Table VI: Progesterone values in 20 serum samples drawn between 3 and 7 days prior to onset of menstruation in women after immunization with the vaccines along with prevailing anti-hCG titres

Sample No.	Progesterone (ng/ml)	Anti-hCG titre (ng/ml)	% hLH cross-reactivity
1	9.0	640	52
2	8.2	600	62
3	3.6	585	70
4	8.3	85	32
5	9.5	145	66
6	17.2	118	64
7	7.4	270	38
8	10.4	420	43
9	12.1	47	54
10	10.0	95	52
11	23.5	275	64
12	11.4	202	83
13	27.5	55	60
14	7.3	90	25
15	11.5	190	51
16	3.7	88	45
17	7.4	90	40
18	8.8	195	61
19	8.1	195	45
20	9.4	45	36

Antibody Response

Every woman immunized with the vaccine generated antibodies reactive with hCG. Table IX gives the mean peak titres obtained with the three formulations. The characteristics of the antibodies are reported elsewhere (10). The antibodies had high affinity for hCG and were effective in neutralization of hCG bioactivity in vivo and in vitro. At 52 weeks, anti-hCG levels were less than 20 ng/ml in 62 out of 88 subjects and in the remaining 26 subjects, titres declined to less than 20 ng in the next 2 to 12 months' time, indicating the reversibility of the immunization. Antibody titres required to prevent pregnancy have been computed to be 20 ng/ml (5,11). In every woman immunized with any of the vaccines, the titres were well above this threshold. For formulation B and A, the mean duration of antibody levels above 20 ng was 34 to 37 weeks. The duration with M was comparatively shorter (17-20 weeks).

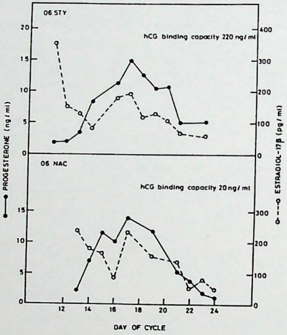

Figure 1: Serum estradiol and progesterone profiles during luteal phase in subjects 06-STY immunized with B-500 and 06-NAC immunized with A-500. Anti-hCG titres during the period are also given.

TABLE VII: Haematological investigations (mean + SD).

Centre code	Weeks	Hemo-globin (g%)	Platelets count/mm³ (thousands)	Packed cell volume (%)	Total lymphocyte count/mm³ (thousands)	Differential leucocyte count (%) Neutro-phils	Lympho-cytes	Monocytes	Eosino-phils
2	0	12.2+2.5	281+26	41.0+5.2	5.2+0.7	45.2+8.4	49.4+7.8	1.4+0.6	3.9+1.7
	24	11.5+0.9	277+15	40.0+2.6	5.5+0.5	46.4+5.7	48.0+5.0	0.9+0.7	4.3+1.9
	52	11.8+0.7	272+11	40.5+1.5	5.7+0.4	48.0+6.0	47.2+5.9	0.9+0.6	3.9+1.3
		(11.5-16.0)	(150-450)	(37-47)	(4-11)	(50-70)	(20-32)	(0-5)	(2-6)
3	0	11.4+1.0	235+32	53.3+5.9	6.5+1.0	62.2+3.6	35.4+3.5	0.3+0.5	2.2+1.1
	24	11.4+0.8	226+24	53.5+5.2	6.3+0.9	60.9+5.0	35.8+4.6	0.4+0.8	3.1+2.2
	52	11.2+0.9	237+39	51.1+5.7	6.5+1.0	61.9+3.7	35.5+3.7	0.3+0.8	2.6+1.2
		(11.5-16.0)	(150-450)	(37-47)	(4-11)	(50-70)	(20-32)	(0-5)	(2-6)
4	0	12.5+1.2	313+40	38.0+4.2	9.2+2.6	65.4+5.0	28.1+3.6	0	6.5+2.8
	24	12.4+1.6	294+49	34.5+2.2	8.6+1.8	66.8+4.4	27.0+3.7	0	6.2+2.5
	52	12.4+1.4	290+35	36.2+3.3	9.2+2.0	67.6+5.8	27.6+4.7	0	6.1+2.8
		(12.0-14.0)	(150-400)	(35-47)	(4-11)	(40-75)	(20-45)	0	(1-6)
5	0	10.8+1.1	171+19	39.2+3.4	7.8+1.3	61.8+5.8	30.9+6.6	0.9+1.1	6.7+3.4
	24	10.9+0.8	170+16	38.8+2.8	7.4+1.1	59.5+6.2	36.6+6.1	0.7+0.6	3.6+2.4
	52	11.0+0.6	176+18	40.4+3.1	7.9+1.7	58.3+9.6	34.9+8.9	1.1+1.1	5.6+3.3
		(10.0-14.0)	(150-250)	(42-48)	(6-10)	(60-70)	(20-30)	(1-4)	(2-6)
6	0	12.4+0.7	160+12	37.3+2.0	5.7+1.4	65.8+6.5	31.2+6.6	1.6+1.0	2.7+1.3
	24	12.1+1.4	171+38	36.3+4.1	7.4+2.9	66.7+9.0	29.3+6.3	1.9+1.8	2.8+1.2
	52	12.1+1.2	159+30	36.4+3.3	6.2+2.3	67.0+6.4	29.2+5.7	2.2+1.2	2.0+1.0
		(11.5-16.0)	(150-450)	(37-47)	(4-11)	(50-70)	(20-32)	(0-5)	(2-6)

Normal laboratory values are given in parenthesis.

TABLE VIII: Clinical chemistry parameters (mean + SD)

Centre code	Weeks	Bilirubin mg%	SGOT IU/L*	SGPT IU/L*	Alkaline phosphatase IU/L*	Urea mg%	Creatinine mg%	Cholesterol mg%	Glucose mg%
2	0	0.6+0.2	6.1+2.1	4.1+1.3	25.7+6.2	22.4+5.6	1.4+0.3	148.5+25.9	71.0+9.0
	24	0.6+0.1	6.5+1.6	4.9+1.1	26.8+4.9	22.3+4.2	1.5+0.3	150.6+22.0	70.9+9.2
	52	0.6+0.1	7.2+0.9	5.9+0.7	26.9+3.5	23.9+2.6	1.4+0.2	149.8+18.0	72.1+6.5
		(0-1.0)	(5-25)	(2-15)	(20-48)	(15-43)	(0.5-1.1)	(150-250)	(70-110)
3	0	0.6+0.1	6.6+1.7	4.6+1.5	30.8+8.4	25.1+5.0	1.2+0.3	147.8+15.3	75.8+11
	24	0.6+0.1	6.8+1.4	5.4+1.2	30.7+6.7	25.2+3.9	1.2+0.2	147.0+12.7	75.3+8.4
	52	0.6+0.1	7.2+1.2	6.2+0.9	29.2+4.9	25.1+2.9	1.2+0.2	148.9+10.9	78.4+8.9
		(0-1.0)	(5-25)	(2-15)	(20-48)	(15-43)	(0.5-1.1)	(150-250)	(70-110)
4	0	0.6+0.1	12.2+3.0	10.9+5.8	51.2+14.8	12.4+2.6	0.7+0.1	211.7+48.1	83.4+13
	24	0.7+0.1	13.2+2.5	8.3+3.5	43.5+9.9	12.7+2.1	0.7+0.1	177.2+33.2	98.8+19
	52	0.6+0.1	14.2+3.4	9.4+2.9	50.1+11.6	12.1+1.9	0.7+0.2	184.3+28.3	93.3+13
		(0.3-1.0)	(7-26)	(5-25)	(23-80)	(10-20)	(0.5-1.3)	(150-250)	(60-100)
5	0	0.3+0.2	11.6+6.5	10.5+6.8	5.2+1.7	16.7+8.5	0.9+0.4	192.5+35.4	81.8+20
	24	0.3+0.1	12.9+8.1	11.3+5.3	4.7+1.4	21.0+5.3	1.0+0.3	209.4+31.5	80.3+13
	52	0.4+0.2	13.9+8.1	12.0+7.3	5.3+1.7	18.7+5.5	1.1+0.2	222.1+29.5	81.5+13
		(0-1.5)	(5-40)	(5-35)	(3-13)	(14-47)	(0-1.2)	(150-250)	(60-90)
6	0	0.5+0.1	42.4+7.3	39.0+8.7	38.4+9.3	20.9+3.2	1.2+0.3	160.7+17.1	93.5+6.9
	24	0.5+0.1	38.6+6.9	38.8+9.6	39.0+11.3	22.7+6.4	1.3+0.4	158.2+13.1	95.3+12
	52	0.5+0.1	37.3+6.3	40.1+8.6	43.3+13.6	23.0+9.1	1.4+0.4	162.9+11.9	98.1+8.4
		(0.3-0.6)	(30-60)	(20-54)	(20-60)	(15-40)	(1-1.5)	(145-230)	(80-100)

* KA units (centre 5), u/L (centre 6). Normal laboratory values are given in parenthesis.

TABLE IX : Anti-hCG titres in women immunized with three vaccine formulations

Formulation	n	Peak anti-hCG titres (ng/ml) Mean + SEM
A	29	322 + 75
B	29	392 + 115
M	30	136 + 65

Coincident with anti-hCG response, the vaccine also produced an elevation of anti-TT in previously immunized subjects or induced response as a result of primary immunization with TT-conjugated vaccine (Table X). The antibody titres were high in most of the women and persisted above protective level over 52 weeks of observation. Women receiving CHB-conjugates also had anti-CHB antibodies.

TABLE X: Anti-TT and anti-CHB response in immunized subjects

Formulation	Peak titres (units/ml) (range)	
	Anti-tetanus	Anti-cholera
A	150 - 7800	45 - 1500
B	95 - 5300	-
M	380 - 3300	40 - 1850

DISCUSSION

In a comparative phase I clinical trial with 3 different formulations of beta-hCG vaccines, A, B and M, none of the 88 subjects reported any serious adverse side effects during one year of observation. About 28% of the subjects immunized with the vaccines complained of minor reactions such as erythema, pain at site, fever and joint pain after the first injection. However, reactions such as pain at site and fever

were also reported by some subjects (23%) enrolled in the control group. The complaints were not repetitive in nature and not in the same subject.

Immunization with the three vaccine formulations did not significantly alter the menstrual regularity (12). This is in conformity with the previous findings that women immunized with beta-hCG-TT and having antibodies partially cross-reactive with hLH, continued to ovulate normally and menstrual regularity was maintained (1,3,6). The mid-luteal progesterone values and the hormonal profiles as indicated by progesterone and estradiol levels also indicate normalcy of ovulatory cycles and confirms the previous observations (1,3,6). Neither the haematological parameters nor any of the metabolic parameters including liver and kidney function tests revealed any change following immunization.

Taken together, the results of the present study demonstrate that immunization with three different types of beta-hCG-based vaccines did not produce any adverse effects. In every case, immunization produced antibodies reactive with hCG along with antibodies against TT and CHB. The antibody response was reversible; the mean duration of antibody levels above 20 ng per ml was 34 to 37 weeks for the B and A formulations and the antibodies were effective in neutralizing hCG bioactivity in vivo (10). Formulation A and B were comparatively more immunogenic than formulation M.

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TWO VACCINES UNDER CLINICAL TRIALS FOR CONTROL OF FERTILITY AND REPRODUCTIVE HORMONE DEPENDENT CANCERS

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Clinical trials are in progress on two vaccines. Both of them were initially designed to control fertility. It has however been found that these are also useful in the treatment of reproductive tract hormone dependent cancers. Human chorionic gonadotropin (hCG), a product of trophoblasts and marker of early pregnancy, is also synthesized and secreted by a number of tumor cells. hCG is an oncofetal protein. Evidences are available for this hormone or one of its subunit to be a growth factor for proliferation of human lung cancer cells. Vaccination against this hormone can thus intercede in the autocrine function of the hormone and curb the growth of the cancer cells. Similarly a large percentage of carcinomas of the prostate are dependent on androgens. Testicular androgens are, in turn, regulated by gonadotropins under the control of gonadotropin releasing hormone (GnRH). Any immunization strategy which can inactivate these hormones, would also have influence on hormone dependent growth of benign as well as cancerous cells. In this presentation, it is intended to describe the clinical trials on two vaccines, one against hCG and the other against GnRH. One set of trials are to achieve contraception. The same vaccines have advanced to the clinical trials stage for immuno-therapeutic intervention in hormone dependent cancers.

COUNTER hCG VACCINE

In early 70's, the choice of hCG as a target for development of birth control vaccines was based on considerations that this hormone is an early signal of

pregnancy, it is made in substantial amounts by the preimplantation embryo and it has a critical role in establishment and maintenance of pregnancy. The hormone was available in purified form. Moreover, its molecular composition and the primary sequence of its subunits was known. Two different approaches emerged to induce antibody response against this hormone. While we proposed the use of the entire ß subunit of hCG,[1] another group advocated the carboxy-terminal peptide (CTP) of ßhCG.[2] In our own experience, CTPs, even though devoid of cross-reaction with hLH, had poor immunogenicity.[3,4] They demanded the use of strong adjuvants and the antibodies generated had relatively lower capacity to neutralize the bioactivity of the hormone. This was ascribable to a limited number of epitopes in the peptide.[3] Another difference in the the initial stage of the two approaches was that we advocated the use of a carrier protein[5] whereas Stevens[2] proposed chemical modification to overcome tolerance to a "self" peptide.

The first prototype vaccine proposed by us consisted of ß subunit of hCG linked chemically to tetanus toxoid (TT).[5] This vaccine was adsorbed on alum, the only adjuvant approved for human use at that time. After due experimental and safety studies,[6-9] probing clinical trials with this vaccine were undertaken to determine whether the conjugate was indeed competent to induce anti-hCG response in women. These early trials demonstrated the ability of this "structured" vaccine to induce antibody response.[5,10,11] The response was

reversible and no side effects of any significance were observed. These findings were confirmed by probing trials on the same vaccine conducted by the International Committee for Contraception Research of the Population Council at Helsinki, Uppsala, Santiago and Bahia.[12]

The limitation of this vaccine was the high variability of antibody titres amongst individuals and those with insufficient titres were not protected against pregnancy. Further research was undertaken to improve the immunogenicity of the vaccine. An adjuvant, sodium phthalyl derivative of lipopolysaccharide (SPLPS), was incorporated in the first injection.[13] Another change made was to enhance the intrinsic immunogenicity of ßhCG, taking cognizance of the fact that hCG assumes a bioactive conformation only when the two subunits, alpha and ß are associated. Individual subunits loose the native conformation to a large extent and are not recognized by the receptors on the target tissues. Association with human alpha subunit had the risk of immunological cross-reactivity with human follicle stimulating hormone (FSH) and thyroid stimulating hormone (TSH). Advantage was taken of the fact that alpha subunit from heterospecies, such as ovine, retained the capability of associating with ßhCG without manifesting the immunological cross-reactivity with the human alpha subunit. The complex alpha-oLH-ßhCG, a heterospecies dimer (HSD), had even a higher steroidogenic potency than the native hCG in Leydig cell system.[14,15] Antibodies induced by HSD were

superior to those induced by βhCG for neutralization of bioactivity of the hormone.[15] Thus one of the formulations indicated by these researches was HSD linked to carriers (formulation A).

Comparative immunogenicity and safety trials were undertaken on formulation A and βhCG linked to TT (formulation B) besides another formulation (mixture of βhCG and αoLH linked separately to carriers) which in animal experiment had shown promise[16] but was not found to be an equally high immunogen in humans. Two series of phase I clinical trials conducted respectively on 101 women who completed one year or more of follow up (88 receiving the vaccine and 13 vehicle only)[17,18] and 41 (36 receiving the vaccine and 5 vehicle only) have led to the following conclusions :

1. Every woman receiving the vaccine produces anti-hCG antibodies. The peak titres vary from 222 to 6085 ng per ml for formulation A at 300 ug dose level.
2. In each case, the antibody response was reversible and antibody titres declined to near zero levels within a period of 2 years.
3. The affinity constants of the antibodies for hCG was of high order (Ka 10^9 to 10^{11} M^{-1}).
4. While the antibodies had cross-reactivity of varying degree with human LH, no cross-reactivity with hFSH and hTSH was observed in any of the serum samples investigated. The hLH cross-reactivity did not impair

ovulation. Menstrual regularity was maintained; 89% cycles were within normal range (22-35 days).[19]

5. No change in clinical chemistry or hematological parameters were noted as a result of immunization.
6. No immunopathological reaction was observed as a result of immunization. Serum samples were tested for anti-nuclear, anti-DNA, anti-parietal cells, anti-smooth muscles, rheumatoid factor, anti-islets cells, anti-adrenal cortex, anti-thyroid mitochondrial, anti-thyroglobulin and anti-C reactive protein reactivities.
7. Antibodies inactivated hCG bioactivity both, in vitro (binding of iodinated hCG to receptors) and in vivo (hCG induced testosterone production in mice and hypermic response of ovaries in immature rats).[17,20]
8. hCG challenge was given in immunized women starting from day 9 post LH surge. Injections were given on seven days with 500, 1000, 1500, 3000, 6000, 10,000 & 15000 IU of hCG. In control women, hCG was detectable in the morning urine samples everyday following hormone administration; its concentration increased with time. No hCG immunoreactivity was measurable in the urine samples of immunized women bearing antibody titres. The serum progesterone values did not increase in immunized women in the manner that they did in the control women. The extent to which hCG challenge was overcome, varied with the prevailing antibody titres. Women with titres above 300 ng had no prolongation of the luteal phase.

In one of the phase I trials, five women manifested immuno-suppression and did not develop a booster anti-hCG response at the time of booster injection. Carrier mediated hapten specific immunosuppression has been observed in mice.[21] This was the first human observation of the phenomenon. An alternate carrier strategy was adopted which evoked anti-hCG response in the expected manner.[22]

In light of these studies and clinical trials, the most immunogenic vaccine is HSD linked to carrier(s). The use of two carriers in alternate sequence proved to be better than repeat immunizations with a single carrier. Analysis of dose response indicated the use of 300 ug as the dose for immunization.

Phase II Clinical Trials

Phase II trials with this vaccine have started in 3 centres in India with the approval of the Drug Controller and respective Institutional Ethics Committees. The study would involve 180 women of proven fertility, sexually active and cohabiting with their husbands. Before enrollment in the study, patency of ovulation would be confirmed by progesterone levels in two bleeds taken during the luteal phase at an interval of 6 days. Immunization schedule will consist of 3 primary injections given 6 weeks apart. Booster injection will be given as and when hCG binding capacity per ml antiserum decline to levels below 150 ng (group A) or 75 ng (group B). The vaccine employed will be HSD linked to TT and/or diphtheria toxoid (DT). The women will use

conventional contraceptives till the schedule of 3 primary injections is completed. In women attaining titres above 150 ng or 75 ng, contraceptives will be withdrawn. The women would maintain menstrual diary card and will be followed clinically every month. In cases where cycle will be delayed, pregnancy test will be performed. A total of 1500 cycles will be studied to draw conclusions on efficacy. At the time of writing of this manuscript, 15 women after completing the two cycles of basal observations had received the first injection of the vaccine.

Anti-hCG Immunization in Lung Cancers

A large number of human lung cancer patients produce hCG.[23-25] In many cases, there is discordinate synthesis of alpha and ß subunits. A human lung tumor cell line ChaGO is prevented from progression to anchorage independent growth stage by an anti-sense RNA for alpha-hCG.[26] Cells thus transfected, do not grow as tumor mass in nude mice.[26] Similar results are obtained with antibodies against hCG and its subunits (unpublished data). Preliminary experiments demonstrate that serum of a human subject immunized with HSD linked to TT/DT (formulation A) inhibited about 65% of tumor cell growth at a dilution of 1:1000.

A potent recombinant vaccine to induce high anti-hCG titres has been developed by us recently. The authenticity of ßhCG gene has been verified earlier. It is expressed as an immunoreactive and bioactive peptide.[27-28] The gene for

βhCG linked to an anchored sequence has been employed at the TK locus of vaccinia. This construct has induced in monkeys very high titres of anti-hCG antibodies (1200 to 14000 ng/ml) following two primary and a booster injections. It is intended to employ this recombinant vaccine for therapeutic intervention in human lung cancer patients. No effective chemotherapy is available for the time being for this type of cancer, nor is it amenable to radiotherapy.

COUNTER GnRH VACCINE

GnRH is a decapeptide made by the hypothalamus. It regulates the secretion of pituitary gonadotropins. These in turn act on gonads to generate gametes. They also regulate the secretion of ovarian or testicular sex steroids. Immunization against GnRH can block all these steps.

Early experiments did demonstrate the block of both male and female fertility by immunization against GnRH.[29,30] They however required the use of Freund's Complete Adjuvant (FCA) which is not permissible for humans. The possibility of inducing antibody response against GnRH, employing permissible adjuvants, such as alum, was reported by us in studies where BSA was substituted by TT.[31] Further information on immunodominant epitopes of GnRH was obtained by making monoclonal antibodies[32] and by immunizations employing various sites of linkage to the carrier.[33-35] It was observed that passive or active immunization against this decapeptide can suppress the progression of estrus in dogs. It can inhibit ovulation in rodents and in baboons. In

species where dependence on gonadotropin continues in pregnancy, immuno-interception leads to termination of pregnancy.[36] In baboons too, anti GnRH antibodies have an abortificient effect during very early phases of pregnancy.[37] Male animals immunized with GnRH vaccine with permissible adjuvants manifested reduction of spermatogenesis and reproductive accessory gland function.[38]

The possibility of developing a male vaccine based on anti GnRH immunizations is demonstrated by the above mentioned studies. The approach has however a serious handicap, namely concomitant reduction of testosterone, which will not be acceptable for contraceptive purposes. Ladd et al.[39,40] have worked out regimes of androgen supplements which restore libido and extratesticular needs of androgens while keeping the animals infertile.

Our laboratory has given attention to the possible use of anti GnRH vaccine for treatment of prostatic hypertrophy and carcinoma of the prostate. A semi-synthetic vaccine was made in which glycine at position 6 was substituted by D-lysine. Amino caproic acid was attached to epsilon amino group of lysine and through this spacer, carrier linkage was effected. This conjugate gives consistently high antibody response. Rats immunized with this conjugate show a drastic atrophy of the prostate.[41] Reduction of prostate size is also observed in monkeys (unpublished data). Toxicology studies were carried out in two species of animals of both sexes, which

have shown the safety of immunization procedure. With the permission of the Drug Regulatory Authorities and the Institutional Ethics Committees, Phase I/II clinical trials have started with this vaccine in two major teaching hospitals in India. Early results show the benefit of immunization in some patients. Similar studies have also started in Salzburg under Prof. Julian Frick and at Santa Domingo. Early results in these clinics indicate a marked fall in Prostate Specific Antigen and in density of bone metastasis.

Postpartum Immunization Against GnRH for Prolongation of Anovulatory Cycles

GnRH agonists have recently been employed in 9 post-partum women to observe continued inhibition of ovulation, without any significant side effects.[42] Immunization against GnRH could achieve the same end objective. The advantage will be that only periodical injections will be required and the cost of treatment will be far lower.

Teratology studies were conducted in bonnet monkeys. Mothers immunized with GnRH vaccine, soon after delivery, continue to lactate and feed the infant. The growth of the infants remains similar to those of the control group. No developmental abnormalities of any type were noted. After weaning of the infant, the immunized monkeys have remained anovulatory as determined by hormonal profiles and other criteria, whereas the control monkeys regain cyclicity in course of time. It is planned to start immunization trials in

women in the post-partum phase, in several countries under the South to South collaborative programmes. Other possible uses of this vaccine may be in endometriosis and in post menopausal women. However the benefit if any of such immunization in these two conditions remains to be ascertained.

SUMMARY AND CONCLUSIONS

Two vaccines, one inducing antibodies against hCG and the other against GnRH have been discussed. Laboratory studies coupled with probing clinical trials have led to an optimized formulation for producing antibodies against hCG beyond an expected minimal threshold to protect against pregnancy. Phase I clinical trials conducted in two series on 142 women in several centres in India have shown that the vaccine produces antibodies in each recipient, the antibody response is reversible, the antibodies are effective in inactivating the bioactivity of the hormone and that the immunization is free of any side effects. Women continued to menstruate regularly. No changes in metabolic and endocrine parameters are seen. No immunopathological reactivity of any type is induced by this vaccine. Formulation A (HSD-TT/DT) at 300 ug dose has been selected for phase II efficacy trials which have started in 3 centres in India.

A live recombinant vaccine has been made carrying the gene of AhCG joined to membrane anchored sequence. This vaccine has produced very high titres in monkeys. Clinical trials with this vaccine are planned in 7 countries in human lung cancer patients. Lung cancer cells make hCG. An experimental study shows that the hormone or its subunits have autocrine function in the growth of the tumor cells.

Another vaccine which has reached the clinical trials stage makes antibodies against GnRH. The vaccine is a

synthetic analog of GnRH linked through a spacer to DT/TT. After due toxicological studies and approval of the Drug Regulatory and Ethics Committees phase I/II clinical trials have started on the vaccine in carcinoma of prostate patients in 2 centres in India and one centre in Salzburg and another in Santa Domingo. Early results show efficacy of immunization in some patients. The vaccine is planned to be used in postpartum women to prolong amenorrhea and inter-child interval.

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RU 486 - Misconceptions
Myths and Morals.

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NOTE BOOK

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BIRTH CONTROL

The Vaccine Alternative

by ROBERT KANIGEL

Since India's independence in August 1947, the United States and India have been actively collaborating in scientific research in several areas. This cooperation received a further fillip when Prime Minister Indira Gandhi and President Reagan signed the Indo-U.S. Science and Technology Initiative (STI) during Mrs. Gandhi's 1982 visit to America. The program, which draws on some of the best scientific talent of both countries, covers various areas of frontier research in health, agriculture, weather and materials. The fruits of STI research will benefit not only our two countries, but the entire world. On these pages, SPAN focuses on one STI project.

On a rocky ridge near the historic Qutab Minar, New Delhi, stands a beautiful complex of buildings. In the new National Institute of Immunology (NII) scientists are busy studying the intricacies of the immune system, reproduction and parasites to produce new and more effective vaccines to control population and combat disease. The priority project is to develop a suitable birth control vaccine that was pioneered by its director and his team. It is currently on human trials on 105 subjects in five centers in India. The project has aroused worldwide interest and involvement of foremost scientists in the area of immunocontraception. Another NII vaccine against leprosy is on efficacy trials in two hospitals of Delhi.

The new complex was inaugurated in October 1986. It has a central block of spotlessly clean labs equipped with sophisticated instrumentation, comparable to the best in the world. Here scientists are engaged in high caliber, multidisciplinary research employing synthetic chemistry, DNA recombinant and hybridoma technology. The institute is also working on developing simple color-strip diagnostic tests for quick and early detection of amebiasis, leprosy, hepatitis, typhoid and pregnancy. To help the scientists in their quest, the institute has excellent facilities for laboratory animals. In a separate building, mice of defined genetic background, special strains of nude athymic mice and other lab animals are bred. Another complex with both indoor and simulated natural environment houses the primates.

As a human visitor enters their large outdoor cage, a dozen chattering baby monkeys huddle in a furry mass, then clamber away, as if a single, many-limbed organism, to the far end of the cage. These animals, each between about six months and two years old, represent the next generation of the institute's monkey colony. But even now they furnish data; they are living proof that their parents were once fertile—key evidence, should their parents later prove infertile, for the worth of the contraceptive that presumably made them so.

A contraceptive vaccine is the prize sought by G.P. Talwar, director of the institute, his collaborators in the United States, and other researchers in both countries working under the auspices of the Indo-United States Science and Technology Initiative (STI).

Talwar supplies a sobering perspective. It took the human race until 1957 to reach the 3,000 million population mark, but the second 3,000 million will take only until the end of this century. Ninety percent of the increase, he points out, will come in developing countries like India. "That will impose tremendous pressures for food, clean water, shelter, education and jobs." Talwar sees overpopulation as an epidemic not unlike the tetanus, diphtheria, or smallpox epidemics that once ravaged humankind. And it can be defeated, he declares, the same way—by a vaccine.

In Talwar's vision, shared by other STI scientists pursuing this research tack, a single injection might grant infertility for six months, a year, two years. A booster could extend that; otherwise, fertility would return naturally. With a vaccine, there would be no remembering to take a pill. No surgery. No struggling with a condom. Pregnancy would be warded off with the same powerful immunological weapons the body uses to fight disease.

When a bacterium, say, or a virus, enters the body, the immune system raises antibodies to it. The antibodies lock onto specific parts of the foreign substance, called an antigen, neutralizing it, and setting it up for ultimate destruction.

Why not, the thinking goes, use antibodies to similarly neutralize a hormone or other protein essential to reproduction?

For sperm and egg to unite, a complex array of hormonal messengers—each, as it were, the "weakest link"—must work together flawlessly. Interrupt, shortcircuit, disrupt, or otherwise interfere with any of them and infertility can result. Doing that immunologically, through antibodies to hormones or tissue components, is the strategy common to all three STI contraceptive projects.

For Talwar, and his collaborators at the New York-based Population Council under chief C. Wayne Bardin, the targeted hormone is luteinizing hormone releasing hormone, or LHRH. A product of the brain's hypothalamus, LHRH orders the pituitary gland to secrete luteinizing hormone and follicle stimulating hormone; in males, that leads to the production of sperm.

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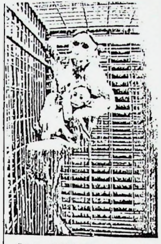
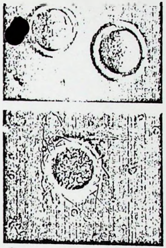
→LHRH
male vaccine



Facing page: G.P. Talwar (sitting), director of the National Institute of Immunology (NII), and researcher Anil Suri discuss the birth control vaccine project. Above: The vaccines are first tested on monkeys of proven fertility who are kept under long-term observation to check return of fertility on the decline of the antibodies, and normalcy of the progeny.



Above: Scientists at the NII are now working on the next generation of birth control vaccines. Antibodies against a protein identified by the institute prevent the attachment of sperms to the egg, surrounding it like a protective layer (top). In the absence of the antibodies, the sperms attach to the egg (below) and fertilize it.

Block LHRH and you would sever that hormonal chain.

Block it how? By raising antibodies to it. The antibodies would mask the LHRH signal. Sperm production would grind to a halt. So would testosterone production. Maintain sexual drive through testosterone supplements and you would have the basis for an effective male contraceptive.

Of course, getting so straightforward a concept to work is another story. Normally, the immune system is triggered by substances it identifies as foreign. But why should it deem foreign LHRH—which is, after all, produced naturally in the body? Reading it as "one of ours," the body has no reason to attack it, and normally won't.

Unless, that is, it's tricked into doing so.

The Talwar-Bardin strategy under STI has been to fool the body into responding to LHRH as if it were foreign. One approach was to make from scratch a molecular variant of LHRH that might be seen as foreign enough to marshal defenses against. Once activated, the body would raise antibodies not just to the new and different parts of the synthetic molecule but to those common to LHRH itself.

Talwar's lab synthesized a number of such LHRH variants. "It was very elegant," he says, referring to their biochemical tinkering. "It would have been the first workable synthetic vaccine." Except that none of them worked; they gave only weak or nonexistent immune response. "Once you produce the antibodies, it's molecular science," Talwar smiles ruefully. "Until then it's an art. We still don't know all the rules of the game."

So Talwar and his American collaborators, including Yun-Yen Tsong and Rosemarie Thau, who work with Bardin at the Population Council, took a safer tack. "Scientists are dreamers. But they are also realistic," says Talwar. "So we went to our old ally—tetanus toxoid."

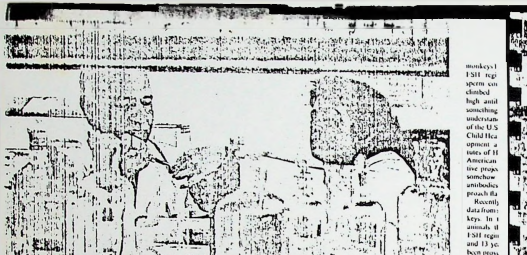
Tetanus toxoid, a component of tetanus vaccine, is well known to provoke a strong immune response and well established as harmless to humans. What if LHRH were molecularly linked to tetanus toxoid, and this new, composite molecule used as a vaccine? The tetanus toxoid would fire up the immune system, spurring the production of antibodies to numerous sites on the composite molecule, among them the LHRH.

The collaborators found that just how and where LHRH was linked to tetanus toxoid made a big difference in the strength of the immune response. Biochemically link it at one end, and it had one effect; at the other end, or in the middle, or somewhere else, and it had quite another.

Ultimately, through one bit of immunological legerdemain or another, they succeeded in generating high enough antibody concentrations to make rats infertile, leaving a scaling up to monkeys as the next step. "The principle works," says the Population Council's Tsong. "We just have to find a good immunogen"—the ideal immune system trigger for LHRH.

Whatever an LHRH vaccine's potential as a contraceptive, Talwar notes, it may have other applications as well. Carcinoma of the prostate depends on testosterone. So does precocious puberty. Today, only castration can treat these conditions. An LHRH vaccine would achieve the same effects through what Talwar calls "immunological surgery."

Of course, as a contraceptive vaccine, this effect on testosterone production has a drawback, it makes maintenance of the sex drive depend on supplementary testosterone. But what if you could interfere in the male reproductive system further along the hormonal chain? Let LHRH be; let it trigger release of both luteinizing hormone and follicle



stimulating hormone, or FSH. Then come in and immunologically block FSH which stimulates sperm production, but has no effect on libido. Such a vaccine might offer the advantages of an LHRH vaccine yet avoid its shortcomings.

Among those trying to develop such a vaccine are STI collaborators N.R. Moudgal and Madhwa H.G. Raj. Once, Madhwa Raj was Moudgal's graduate student at the Indian Institute of Science in Bangalore. Sometimes, Madhwa Raj reproduces, he would utter a moan-y for an experiment by leaving a banana out on the veranda. That was back in the 1960s. Then came a postdoctorate at Harvard, a faculty slot at the University of North Carolina in Chapel Hill, and finally a professorship at the Louisiana State University, where he now heads the reproductive endocrinology section.

Above: Rose research in the minister's laboratories helps in developing new vaccines. Here Archana Kapur, a scholar working for her PhD, discusses her work with Ishwar Bapat. Both cancel vaccines as well as oral STI are currently being tested at various institutes in the country.

Today, through the Science and Technology Initiative, Madhwa Raj once more collaborates with his old mentor, Moudgal, who directs the Centre for Advanced Research in Reproductive Biology at the Indian Institute of Science. Moudgal's monkey colony, with some 400 animals housed in clean, well ventilated cages—no more bananas on the veranda—is one of the largest of its kind in the world devoted entirely to research.

Back in the late 1970s, Madhwa Raj and Moudgal had independently shown that neutralizing FSH immunologically could indeed inhibit sperm production in immature rats and that, as anticipated, it left testosterone production and libido alone. Those early studies were based on passive immunization, the antibodies were supplied to the body artificially. Then they scaled up from rats to monkeys and from passive to active immunization—true vaccination, in which the body's immune system makes its own antibodies after being kicked on by an antigen. So far, so good.

Then came the Nieschlag bombshell.

E. Nieschlag, a West German who had earlier confirmed the Madhwa Raj and Moudgal results, in 1983 reported that in monkeys he had kept on an anti-FSH regimen for four years, sperm counts had inexplicably climbed higher despite still-high antibody levels. This is something that is difficult to understand," says Gabriel Bialy, of the U.S. National Institute of Child Health and Human Development at the National Institutes of Health, manager of the American half of the contraceptive project. Were the monkeys somehow overriding the STI antibodies? Was the whole approach flawed?

Recently, Moudgal reviewed data from some of his old monkeys. In the colony were four animals that had been on the FSH regimen for between seven and 13 years. All had originally been proved fertile. All had been left infertile by the FSH vaccine. All, from time to time over the years, had received booster shots. Now, he compared them to control animals of about the same age. One control, No. 309, had a sperm count per ejaculate of 140 million, about normal. The immunized No. 308 had a sperm count of virtually zero. Results for the other three old monkeys were similar. Those four oldtimers, someone told Moudgal, "are the best evidence you have."

Why the discrepancy between Moudgal's data and Nieschlag's? One difference, Moudgal speculates, is that Nieschlag used theses monkeys, while he used bonnets. Bonnet monkeys get their name from a distinctive crown of hair on their heads. But their differences from rhesus monkeys are not just cosmetic. Whereas the rhesus is fertile for six or seven months and then stays so be fertile from about April to around the end of August, the bonnet is fertile year round. In this respect, argues Moudgal, bonnet monkeys are just like humans, making them a more appropriate model.

The FSH vaccine works. With it, sperm counts normally 200 million or so per ejaculate, drop to five or two or one million or less—low enough in the case of humans to grant de facto infertility. But is that good enough? What if messing with normal sperm production made the few sperm left abnormal? The fear is not an occasional pregnancy, but rather that any resulting fetus might turn out deformed. Accordingly, many in the field demand that any male contraceptive achieve not just low sperm production, or oligospermia, but zero sperm production, azoospermia.

Madhwa Raj, however, disagrees. Sperm in their ejaculate or not, monkeys immunized against FSH, he says, just don't seem to get normal females pregnant. Just why hasn't been another area of collaboration with Moudgal under STI. In one visit to Moudgal's lab in July 1985, Madhwa Raj found that sperm

"Once you produce the antibodies, it is molecular science Until then it is art."

from immunized monkeys failed to bind to the egg. Photos from that test tube study show one egg enveloped in a dense thicket of normal sperm, another almost denuded of sperm from an immunized monkey. Perhaps, Madhwa Raj wonders, the FSH vaccine does not just slash sperm production by a hundredfold, but also reduces the ability of those sperm that are made to recognize, bind with, or otherwise complete the fertilization of the egg? Perhaps, in Madhwa Raj's phrase, it makes them "subfertile." He does not know. "I'm approaching it with an open mind," he says. "I don't know where all this will end."

The thick coat surrounding the egg through which the sperm must migrate in order to successfully fertilize it is called the zona pellucida, the target of a third STI collaboration in contraceptive vaccine development. Normally, explains STI researcher Bonnie Dunbar of Baylor College of Medicine in Houston, sperm sticks to the zona like flypaper. But if a woman had antibodies to her own zona, it might then no longer show affinity for the sperm, thereby inhibiting fertilization.

In fact, some women known to be infertile have been shown to have their own, natural antibodies to zona antigens. And some animal studies hint that development of immunity to one's own zona may be a natural part of development of ovarian follicles, in which eggs mature.

Dunbar came away impressed with the monkey colonies she saw at Chandigarh. She heard the joke, "The students may starve here but the monkeys are fed." And it was true. "The rhesus monkeys which have been immunized with the ZP preparation," she wrote of her visit in January 1986, "were of the healthiest kind I have seen in captivity and the experiments have been carried out rigorously and precisely."

Much of the work was, necessarily, methodological—setting up the assays, troubleshooting problems as they came up. A problem collecting sperm from the rabbits? Try doing it. Dunbar suggested, with the animals still in their cages on familiar ground. Certain gels, used to separate proteins, were not gelling? Change the amount of catalyst you are using. That suggestion , alone, Dunbar guesses, saved months of tedious work.

Small gains, in an ambitious project that Dunbar realizes will take years to bring off. In the early excitement over the promise of a zona-based contraceptive, she recalls, someone had predicted they would have one within seven years. "Well," she says, "that was seven years ago. And we are still doing the basic biochemistry."

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reliable ovulation predictor—require only the conventional incentives of the marketplace. There is no dearth of market incentives for antiviral drugs, and research in this field is burgeoning. If usefficacy against the AIDS virus can be demonstrated, the FDA is likely to expedite marketing of such an agent. An ovulation-prediction test faces only straightforward FDA barriers, typical of any new diagnostic method, and no toxicity expenses (since only a few drops of urine, saliva, or blood are required).

The other four approaches, however, have certain handicaps, the elimination of which will require major legislative or social changes. (i) They will be used by healthy people—a circumstance for which society tolerates very little risk. (ii) Development times covering one or two decades make any investment extremely risky, be it a company's money or an investigator's career. If initiative and support were to depend on nonprofit or governmental agencies, long-term commitments would have to be made. (iii) Until now, only large, multinational pharmaceutical companies have had the resources and expertise for drug developments of the magnitude of these four contraceptive approaches. Given the long development time, recovery of the investment and generation of profit require a long proprietary position, which the present patent laws do not offer (*48*). (iv) The legal exposure to liability suits could be extremely risky. Impotence or prostatic cancer—two conditions commonly associated with aging in males—are likely to attract litigation by men who may take their pill for 40 years and then blame it for their misfortune. Cases of permanent sterility would likely be attributed to an antifertility vaccine if millions of nulliparous women opt for such a method of birth control. (v) Large pharmaceutical companies, selling many products and having many stockholders, are likely to be more sensitive to threatened boycotts and political pressures than smaller companies. A menses-inducer may well fall victim to a fear of such pressures, even though it may be the most efficient way to reduce abortions.

How can the hurdles be cleared that now stand in the way of a contraceptive revolution or even of modest progress? History demonstrates that no major advances will occur without the participation of the pharmaceutical industry—in production, distribution, development, and even research. The idea that such decisions should be left to the marketplace is useless, for the market has already spoken: given the cost, time, and litigation risks, it is not worthwhile to invest in the development of new contraceptives. A survey of leading R&D therapeutic categories for 1988 (*49*) does not list contraceptives even among the first 35 rankings. If society wants a well-stocked contraceptive supermarket, society will have to provide the impetus. Of all incentives, addressing the litigation problem in the United States would be of overriding importance. In fact, this is precisely the area where some moves have finally been initiated by legislators prompted by the crisis in vaccine production and the even bigger need for R&D of new vaccines for infectious diseases, from AIDS to malaria (*50*). Strangely, the similarity in the problems faced by the developers and producers of vaccines and most contraceptives has not yet been recognized in legislative circles.

Modification of Product Liability

The National Childhood Vaccine Injury Act of 1986 was introduced by Congressman Henry A. Waxman and constitutes a form of no-fault insurance against possible injuries from the seven pediatric vaccines (*51*). The rationale for this limitation was that all children must receive such vaccinations to attend school and that a few are bound to be harmed by such compulsory vaccination. Manufacturers of these vaccines threatened to withdraw from the field because of ever-increasing liability suits, and the Waxman bill was designed to stem such a crisis in vaccine production. Revenues come from a special tax imposed on any childhood vaccine. Like any insurance system, the beneficiaries are expected to pay the premium for risk protection.

The Waxman bill does not address itself to the problems of other vaccines, whose administration is not obligatory, nor does it pay attention to the even more serious problem associated with the development of new vaccines. It took another national calamity, the AIDS epidemic, and the public's interest in an AIDS vaccine for the California legislature to examine remedies to the product liability barrier standing in the way of vaccine research. The bill introduced by Assemblyman John Vasconcellos (*52*) is specifically limited to AIDS and applies only to California. However, it represents a promising model for federal legislation covering other vaccines and, as I wish to emphasize, also for contraceptives.

The key provisions of the California bill are that such a vaccine is recognized as "unavoidably unsafe" and thus exempt from strict liability lawsuits. The bill's key feature of restricting the manufacturer's liability and of funding compensation for medical costs, loss of earnings, and pain and suffering out of an extra charge imposed on the price of the vaccine, would be essential in the contraceptive field. Improvements can be made in these legal models (*53*), notably a further restriction of tort law application, which is opposed by trial lawyers' lobbies, as are most other provisions of these bills.

Contraceptives and vaccines are obvious targets for superlitigation, because they are not curative drugs to be taken by people already ill; they are administered to healthy people to prevent a condition that the person may never get. Even though a no-fault insurance program, structured around self-funding, would be the single most important incentive for the gradual reentry of the pharmaceutical industry into the field of contraceptive innovation, there are differences in perception between vaccines and contraceptives that operate against extending any special incentives to the latter class.

The societal and personal costs of an undesired pregnancy and of an unwanted child are simply not equated by the public to the immediately evident health consequences of a disease, be it measles or AIDS. Among some groups in the United States, contraception is inherently suspect because of its actual or perceived effect on sexual mores. Finally, U.S. society is likely to look askance at incentives that, directly or indirectly, may benefit pharmaceutical companies, when such firms are generally among the most profitable sectors of U.S. industry. But when another decade or two of minor improvements of existing methods, or even of diminished contraceptive choices, has passed, and the number of abortions, legal or illegal, has not dropped significantly, when this bitter pill is tasted by the next generation, then the time may be ripe for substantive changes.

Conclusion

In view of the present political and social climate in the United States, and the minimal participation of the pharmaceutical industry in contraceptive development, all we can expect well into the beginning of the 21st century are minor modifications of existing methods: different delivery systems for steroids, possible improvements in sterilization techniques and barrier methods, more precise indications of the safe interval, and possibly a more realistic reconsideration of the IUD option. Such modest developments will extend contraceptive use patterns, but they will not affect our total dependence on conventional 19th- and 20th-century approaches to birth control.

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The Bitter Pill

Carl Djerassi

Fundamentally new approaches to birth control—for example, a male pill, a once-a-month menses inducer, and an antifertility vaccine—cannot be realized before the next century, and then only if the virtual withdrawal of the pharmaceutical industry from this field can be reversed. Major changes in product liability would be the most significant incentive.

In 1951, when our research group in Mexico City accomplished the first synthesis of an oral contraceptive (*1*), Mexico had 28 million inhabitants (*2*), it now has 86 million and has risen to 11th rank among the most populous countries. Mexico City is the largest city in the world and by the turn of this century its population will probably equal that of the entire country in the year of the pill's first synthesis.

The population growth of Mexico after World War II is not unique. In 1923, the year of my birth, the world's population was 1.9 billion. On my 65th birthday, it had exceeded 5 billion and at the present growth rate will reach 8 billion on my 100th birthday (*3*). Today the populations of Europe and Africa are virtually identical, approximately 500 million each. In just 35 years—in spite of famine and disease—Africa's population will triple unless the acquired immunodeficiency syndrome (AIDS) epidemic interferes with conventional demographic predictions. Europe's population will stay essentially the same.

Yet this is not the bitter pill of my title, which refers to the fact that the United States is the only country other than Iran in which the birth control clock has been set backward during the past decade. The quality of birth control in the United States is not likely to change by the year 2000, with the consequent likelihood that there will be no significant reduction in the number (1.5 million) of abortions that now take place annually in the United States. Indeed, the contraceptive choices in the United States at the end of this century may be even more limited than they are now.

Introduction of Steroid Oral Contraceptives

Until the introduction of the birth control pill in the early 1960s, abortion (then illegal in all but a few countries) was virtually the only available method of birth control separated from coitus. In my opinion, it was this property of the pill and the privacy it offered a woman, rather than the pill's efficacy, that made its initial acceptance so rapid. By the end of that decade, the cumulative decisions of nearly 10 million American women had made the pill the most popular method of birth control.

Yet even now, almost three decades later, epidemiological reports regularly include the debate as to whether prolonged use of the pill increases the risk of breast cancer (*4*). Many women will be discouraged to learn that a conclusive answer will not be available before the turn of this century, because the dosages of both the progestational and the estrogenic components of the pill have been progressively lowered since the middle 1970s. The same reservation also applies to some of the beneficial, noncontraceptive effects of the pill, such as protection from benign breast tumors and ovarian, as well as endometrial, cancers (*5*). Will the protection persist for women taking the lower dosage steroid regimens?

The introduction of the pill into medicine came at the best possible time, and also at the worst. It was a time, before the thalidomide tragedy, when new drugs were rapidly being introduced; pharmaceutical companies, the media, and the public proclaimed and accepted the benefits of the postwar chemotherapeutic revolution. Every problem, be it a medical one or a social one such as the population explosion, seemed amenable to a "technological fix." It also proved to be the worst of times, because the same decade saw three important movements concerned with central issues of contemporary society—women's role in society, environmental protectionism, and consumer advocacy—achieve their aims largely by depending on the unique character of the U.S. litigation system.

The early influential books of the modern feminist movement emphasized the urgent need for improved female contraception. Simone de Beauvoir's *The Second Sex* (*6*) stated explicitly, and Betty Friedan's *The Feminine Mystique* (*7*) implicitly, that a liberated woman must be in control of her own fertility. Probably most women will agree that the pill, more than any other single factor, contributed to that aim. But an informed and highly motivated group of women—primarily American and, by world standards, exceedingly affluent—while emphasizing their abhorrence at male domination, also strongly criticized the pill (*8*) and frequently did so claiming to speak for women all over the world. They were concerned when the first epidemiological studies documented some of the pill's less obvious side effects (*9*). Women, who earlier had objected to being used as human guinea pigs, now asked why the pill had not been tested more thoroughly.

An undercurrent of such feelings persists. Even in the latest edition (1984) of *Our Bodies, Ourselves*, produced by the Boston Women's Health Book Collective, one can find it remarked that "the Food and Drug Administration [FDA] approved the pill for marketing in 1960 without adequate testing or study. . . . The pill became a gigantic experiment: within two years about 1.2 million American women used it . . ." (*10*, p. 237). Such large-scale, post-marketing "experiments" are unavoidable, however, and occur with every vaccine and drug to which a person will be exposed for long periods of time. Only medicines used to treat acute conditions and used over short time intervals can be effectively screened for most side effects during the pre-marketing, clinical test phase. With regard to the question of why it took so long to lower the initial high dosages of the progestational and estrogenic ingredients, it must be remembered that abortion was completely illegal at that time; experimenting with lower dosages might well have led to higher failure rates for which no alternative could be offered to the women on whom the new dosages were tested.

Retrenchment of Pharmaceutical Industry

When in 1970 I wrote *Birth Control After 1984*, I pointed out (*11*) that unless major and largely unpopular changes in public policy were instituted, birth control in 1984 would not differ much from that which existed in 1970. I emphasized that our increasing knowledge of human reproduction and of actual as well as potential side effects, along with women's concern about safety and risk aversion (shared by most of contemporary American society), made it necessary to plan on a 12- to 20-year development period for any new chemical contraceptive agent. At that time, there were 13 major pharmaceutical companies (9 of them in the United States) that conducted research and development (R&D) in contraception; by 1987, the number had dropped to four (only one of them in the United States). Today none of the active progestational and estrogenic ingredients of the pill is manufactured in the United States.

The withdrawal of the large U.S. pharmaceutical companies from contraception R&D (*12*) has had three major causes. The first was the stringent animal toxicology tests (7 years in beagles and 10 years in monkeys) demanded in 1969 by the FDA (*13*) in response to concerns about the long-term effects of steroid contraceptives. These requirements were not modified (*14*) until 20 years later as a result of overwhelming evidence presented by foreign regulatory agencies and the World Health Organization (WHO) (*15*) about the futility of such special "overkill" mandates. Second, the impact of the congressional "Nelson Hearings" (*16*) conducted between January and March of 1970 was exacerbated by the commentary of self-interest groups and further sensationalized by the press, thus giving the contraception field an extremely poor image. The fact that the pharmaceutical industry chose not to testify before Senator Gaylord Nelson's committee, and the subsequent disaster of the Dalkon Shield intrauterine device (IUD), only aggravated the hostility (*17*).

The third blow, and in the end the most devastating, has been the changes in the litigious character of our society during the past two decades, especially where drugs and medical practice are concerned. Unquestionably, the fear of litigation had a salutary impact on some practitioners and manufacturers in medicine in general and on birth control in particular. The Dalkon Shield is a prime example of a case in which litigation was essential. At the same time, contemporary tort law, with respect to legal liability, has altered medical practice for the worse. In the case of contraceptives, litigious practices have been extreme. In 1986, for instance, the Ortho Pharmaceutical Company lost a $5,151,030 judgment in Georgia because its spermicide Ortho-Gynol, used by a woman while she was unknowingly pregnant, was alleged to be the cause of her baby's birth defects (*18*)—a possibility that is not consistent with current epidemiological evidence (*19*). And although in most malpractice and product-liability cases (for example, that of asbestos) the plaintiff recovers no more than one-third of the financial judgment, the remainder being consumed by the legal community (*20*), such litigation has added an enormous financial burden to precisely that segment of the population that the legal system was designed to protect, the consumer.

The impact of litigation on the pill is especially instructive. Indisputably, some women have been physically harmed by the pill, and it is reasonable for society to compensate them in one way or another. Even though few pill suits that have gone to trial have been won by the plaintiffs, the legal defense cost for the drug and insurance companies has escalated to such an extent, especially because of liberalized discovery rules permitting plaintiffs' attorneys to demand tens of thousands of documents, that out-of-court settlement of such litigation is often cheaper than defending it in court. The Office of Technology Assessment (OTA) in its 1982 report (*21*) stated that liability costs in the oral contraception field were higher than for any other drug category. These legal costs are in the end paid for by the millions of women who benefit from the pill and who would probably object greatly if they were returned to the narrow contraceptive options of pre–World War II days. The cost of a monthly regimen of the pill has increased nearly tenfold in the United States during the past dozen years, even though most pills now on the U.S. market have been "off patent" for many years. Fear of litigation and unavailability of insurance has eliminated market competition: until 1988, no generic versions of the pill were available, and even the ones that have appeared recently cover only a fraction of the market (*22*) and are, in any event, manufactured by the producers of the proprietary formulations.

Pill Use in the United States

No new active ingredients have appeared in the pills sold in the United States since the 1960s. By contrast, three new ones (desogestrel, norgestimate, and gestodene) were introduced in Europe in the 1980s (*23*). The leading European manufacturer of the most advanced pill has so far not introduced its product (desogestrel) in the United States—in part because of potential liability exposures (*24*). Yet this product has one of the lowest dosages of all pills and, moreover, has an improved metabolic profile compared to the other progestational steroids currently available to women in the United States (*25*).

The negative publicity of the Nelson hearings (*16*) resulted in both justified and unjustified caution about the pill. Consumption dropped by over 20% to about 8 million women in the United States in the 1970s (although it continued to increase in Third World countries) but then started to rise again to the current all time high of more than 13 million American consumers (*26*). The consensus now is that for healthy young women, the pill is the most effective contraceptive method and probably one of the safest. Women in their middle thirties or older were thought to be at increased risk in terms of cardiovascular complications, and the current pattern of use among such women in the United States reflects these beliefs, although the most recent epidemiological evidence concerning low-dose pills suggests that such risk applies only to heavy smokers (*27*). As a consequence of these concerns, and because of the lack of other effective alternatives, the incidence of sterilization has risen so sharply [in contrast to Western Europe (*28*)] that this essentially irreversible method now surpasses pill use among couples in the United States.

The attitude of feminist activists toward the pill has also changed. Although one can still find occasional anachronisms like the "born-again contraceptive fundamentalism" expressed (*29*) in 1984 by one of the early feminist writers, Germaine Greer (who indicates that she has no use for the pill and even denigrates the diaphragm in favor of coitus interruptus, the cervical cap, and condoms), the current position of most informed feminist spokeswomen toward contraception in general, and the pill in particular, reflects the realities of the 1980s. Like the vast majority of American women, they want for themselves and for their partners more choices, to suit the personal and professional lifestyles of women working outside the home. They want full and up-to-date information on each method. In the case of the pill, this includes dissemination of the potential negative side effects as well as of the more recently discovered noncontraceptive benefits (*5*).

Women are now represented in substantial numbers in decision-making bodies dealing with contraception, such as the advisory committees of the FDA, the National Academy of Sciences, the

The author is professor of chemistry at Stanford University, Stanford, CA 94305. This article is based on the "Gustavus John Esselen Award For Chemistry in the Public Interest" address at Harvard University on 6 April 1989 and is an expanded version of a talk presented at the annual meeting of the Institute of Medicine of the National Academy of Sciences on 19 October 1988.

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Anti-pregnancy Vaccine In Trouble. - By Satyendra Tripathi

The hum of research workers continues as usual at the bio-chemistry department of the All India Instituto of Medical Science here, where several promising projects on fertility control are underway. However, the crucial project which is in advanced stages - the development of an anti-pregnancy vaccine - is in trouble.

Of the two major grants to this project from international agencies one was somewhat abruptly terminated last December and the other one became the target of a a scandalous article published almost simultaneously in the donor country, featuring the views of two scientists whose motives may not be altogether above the board. What is more the two developments are alleged to have some indirect links between them.

The withdrawn grant was from the WHO's Expanded Programme for Research in Human Reproduction (EPRHR) which had been supporting the project since 1972. Initially the grant was of 20,000 dollars a year but the project was accorded high priority in 1976 and its share of the WHO grant to the research and training centre at the AIIMS was increased to 80,000 dollars a year.

What had dismayed Dr. C.P. Talwar, head of the biochemistry department is that two successive expert committees consituted by the EPRHR to review the progress of the project, gave no disapproving indication after their site visits and examination of experimental data in 1976 and 1978 respectively.

While none of the reports of the review panels has been made available to Dr. Talwar, the first committee expressed its satisfaction in no uncertain terms to him and to Dr. V. Ramalingaswami, the then director of AIIMS.

According to Dr. Ramalingaswami, now director general of the Indian Council of Medical Research, it gave a "generally favourable review with some suggestions for further animal trials to test the vaccine's toxicology aspect."

These suggestions he said, were subsequently carried out as far as possible. The second review panel did not communicate its assessment even verbally.

According to Dr. M.A. Belsey, Generva-based senior scientist connected with WHO's research divsion on human reproduction who happened to be in New Delhi, the EPRHR may have cancelled the grant due to misgivings on the clinical trials of the vaccine on human subjects as the data is not yet sufficient to show that the vaccine will not disturb the normal hormone balance in women in the long run.

He said WHO has adopted very rigorous guidelines for clinical trials in projects aided by it to guard against rash experiments of new products on humans. However, he said as he was not directly connected with the EPRHR. he could not be certain as to the actual reasons for the grant's termination.

Dr. Talwar brushed aside this argument on two counts. Firstly, he said the WHO grant was specifically for animal studies and this money was never used for the clinical trials which have been funded by the Family Planning Foundation of India and the trials at six centres abroad were supported by the Population Council of New York.

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In any case if the EPRHR wanted further animal experiments, the termination of its grant for that very purpose would not be the way to go about it, he said.

As for the safety aspects of his vaccine, Dr. Talwar vigorously denied any adverse results in extensive animal trials during the past five years and human trials in the past three years on 63 women conducted in India, Finland, Sweden, Chile & Brazil. ... ■

Indian Express 5th March 1979.

He also pointed out that in all these countries the ethics committees and public health authorities had given clearance for the experiments.

He seems to think that the reasons for the termination of the grant might well be other than scientific, like the interests of a rival American scientist, Dr. Verson Stevens, said to be a protege of Dr A. Kessler who heads the EPRHA.

More than the financial setback, Dr. Talwar is upset about the loss of credibility of his project which could possibly lead to his losing valuable support from other agencies and raised eyebrows among fellow scientists. To clear these apprehensions, he has urged the Health Ministry to register a formal protest with WHO and to call for the review committees' reports for an impartial assessment of his work.

The article referred to earlier, published in a recent issue of a popular Canadian magazine, "Macleans", begins by claiming that trust in his vaccine caused unwanted pregnancies for two women & an abortion for a third subject.

It quotes Dr. Bernhard Cinader, a member of WHO task force for research on human reproduction, and Dr. Stevens to establish that the human trials are not warranted by the available data and portrays Dr. Talwar as a rash scientist.

The article seems to be aimed at a rousing public opinion against the continuation of the dollar 160,000 grant to Dr. Talwar's project from the International Development Research Centre of Canada. It concludes that, "Canada, by contributing funds to Dr. Talwar's work at the AIIMS, New Delhi, seems to be an unwitting accomplish". And that in this project "women will continue to be used as guinea pigs and countries like Canada will face a continuing foreign aid dilemma".

According to Dr. Talwar, the article amounts to a calculated misrepresentation of facts to thwart the progress of the Indian vaccine which he claimed was already patented in 18 countries to the ire of his competitors.

Regarding the allegation about the inefficacy of the vaccine in the three cases, he clarified that these pregnancies had occurred due to carelessness on the part of the subjects.

According to him, every subject is initially given 4 shots of the vaccine at fortnightly intervals followed by an 8-week lag period required for sufficient build-up of anti-bodies which check implantation of fertilised ovum in the uterus. The women were asked to use other contraceptive methods during this period and to come for regular check-ups to determine the anti-body count.

These particular women had failed to use contraceptives in the prescribed period with the unwanted result. He, however, denied his vaccine having ever caused any abortion.

In a sharp rejoinder to the article, Dr. Talwar has challenged Dr. Stevens and Dr. Cinader to confront him on an appropriate scientific forum where he can defend his work, rather than resorting to malicious propaganda in non-scientific magazines. Though the Canadian grant has been recently renewed such attacks during the election year in Canada, Dr. Talwar fears, could cause further setbacks to the programme.

* Abortion, Sans Tears

and prefer natural methods. It has found a foothold in a few other places such as the Philippines, Peru, Sri Lanka, and the Seychelles. Lanctot says there are reports from Zambia that among rural women it "is improving and changing their relationships with their men."

But in most of the family planning community, natural family planning is regarded as ineffective, unpopular, and expensive. Joseph Speidel of the Population Crisis Committee says the dropout rate from programs is about 50 percent, and periodic abstinence is a month. Programs take years to become established, and strenuous educational efforts are required because very few people in the developing world are aware of the fertility cycle. Natural methods are practiced by only 2 to 4 percent of contraceptors in the Third World, and by 5 percent in the United States. It is only used by 0.7 percent of those benefiting from federal family planning programs. The per capita cost in these programs is $473 (largely because of training expenses), compared

The fuss over the policy change is unlikely to aid the cause of family planning efforts in general, which have become increasingly entangled in politics. McPherson has been well regarded by population experts, who believe he is committed to the spread of family planning and doing the best he can in the environment provided by the Administration, which has made curbing abortion the cornerstone of its population policy. However, family planning people have become increasingly dismayed by his willingness to accommodate to pressures

Contraception Research Lagging

While research on natural family planning is finally getting some long-awaited attention, contraception research worldwide has been stagnant for the past 15 years. The U.S. investment has actually declined in real dollars because of a sharp drop in research by pharmaceutical companies.

The Population Crisis Committee reports that global expenditures—over half of which are made by the U.S. government—totalled about $175 million in 1984. Most of this was on basic research in reproductive biology. The total devoted to applied research on contraception is estimated at about $40 million. According to the World Bank, the field could readily absorb a doubling of this amount over the next few years.

Prior to 1970, American pharmaceutical companies led the field in contraceptive research and development, with expenditures of between $15 million and $20 million in 1970, according to Carl Djerassi of Stanford University, who formerly also held two positions as director of research at Syntex Corp. Such research has plummeted by 2000-30 percent. Upjohn and G. D. Searle have recently closed down their fertility research operations. Upjohn had to relocate 30 scientists, and only a few firms remain in the field, according to Djerassi.

Companies have been backing out because of inhibitory federal regulatory policies and the skyrocketing costs of liability insurance. Upjohn has been trying to get Food and Drug Administration approval for Depo-Provera, its 3-month injectable contraceptive, for the past 8 years. Although Depo-Provera is used in 80 countries and has been endorsed by the World Health Organization an FDA panel last year concluded that the safety evidence was not compelling (*Science*, 23 November 1984, p. 950). The FDA will be reconsidering the matter soon, but there is little reason to expect a favorable decision.

Product liability fears are even more compelling. Court awards for alleged damage from contraceptives are extremely high, in part because they are used by a "healthy" population, says Djerassi, and any negative outcomes are blamed on the drug. The industry as a whole has been shaken by the experience of A. H. Robins, which has spent some $300 million in litigation over the ill-fated Dalkon shield and which recently filed for bankruptcy. Gabriel Braly, chief of the contraceptive development branch at NIH's Center for Population Research, relates that development efforts on Capronor, a new biodegradable contraceptive implant, has been halted because researchers were unable to obtain product liability insurance. Because liability expenses are way out of proportion to the size of the market, no company is coming out with a generic oral contraceptive even though patents are expiring on almost all of them.

There have been no dramatic breakthroughs in family planning practices since birth control pills and intrauterine devices were introduced 25 years ago. Sterilization remains the primary mode of birth control in the developing world, followed by abortions, which are performed at the rate of over 40 million annually.

The closest development for the near term is Norplant, an implant developed by the Population Council, which provides contraception for up to 5 years. Used in Finland (where it is manufactured) and Sweden, it has been studied for the past 10 years in clinical trials in this country, and FDA approval is to be sought before the end of the year. If approval is gained as expected, says Wayne Barden of the Population Council, this will be "the first totally new method since IUD's were introduced."

A variety of long-term avenues of research, including new male contraceptives, an antipregnancy vaccine, and reversible sterilization are being pursued. Since it may take two decades between the development and widespread use of a new method, the likelihood of a major breakthrough before the end of the century is virtually nonexistent. Some of the more promising technologies are postcoital drugs and menstrual inducers, but no Agency for International Development funds can go to research on any alleged or suspected abortifacient agents.

There are some signs, however, of a revival of interest in contraceptive development. The National Institute of Child Health and Human Development, which houses the Center for Population Research, has proposed a 4-year "special initiative on contraceptive development" which would quadruple current expenditures—to some $29 million—by 1989. And the World Bank, the World Health Organization, and other international bodies are now seeking to form a global consortium to advance cooperation and stimulate funding in fertility and contraception research.

—CONSTANCE HOLDEN

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Injectable Contraceptive Synthesis: An Example of International Cooperation

Pierre Crabbé, Egon Diczfalusy, Carl Djerassi

Until now pharmaceutical companies have played the dominant role in the field of chemical contraception because of the availability, within one organization, of the wide array of disciplines needed to bring such an agent to the general public (*1*). During the past decade, however, the pharmaceutical industry has reduced, on an absolute and relative basis, its research efforts in the contraceptive field (*2*). This is particularly true with regard to contraceptive methods that would be appropriate in developing countries but of relatively little interest in highly developed ones. For example, there is a great demand for long-lasting, injectable steroid contraceptives in many lesser developed nations, but the only two widely available agents (Depo-Provera and norethisterone enanthate) suffer from several disadvantages, one of these being that, although they were developed in the 1960's, they have still not been approved for general use as contraceptives by the U.S. Food and Drug Administration.

Summary. Since many contraceptives appropriate for use in developing countries are not of major interest to the pharmaceutical companies in developed countries, the World Health Organization has sponsored a program whereby contraceptives are developed outside the traditional pharmaceutical industry channels. This program might serve as a model for the development of other drugs or even pesticides.

Initiation of Program

The development of new injectable contraceptives requires that a concerted effort be made to synthesize novel steroid compounds and subject them to thorough biological evaluation. Since such an effort was not being made by international pharmaceutical companies, the World Health Organization (WHO), as part of its Special Programme of Research, Development and Research Training in Human Reproduction, established a task force to determine whether such a development program could be launched outside the pharmaceutical industry. At a meeting at the WHO headquarters in Geneva in January 1973 (*3*), it was concluded that the development of a new, long-acting contraceptive agent would be worth combining with an effort at institution building in lesser developed countries. In this article we outline the initiation and organization of this program. The results obtained to date suggest that this program might serve as a model for other drug development programs outside the traditional pharmaceutical industry mechanism. For example, the development of drugs for such parasitic diseases as leishmaniasis, schistosomiasis, and onchocerciasis has been neglected by the pharmaceutical industry. A similar approach could also be envisaged for the creation of new pesticides.

In July 1975, a group of internationally recognized steroid chemists (*4*) with past or current experience in the pharmaceutical industry attended a meeting held under WHO auspices at Stanford University. These chemists compiled a list of approximately 150 hypothetical steroid compounds that they considered could be synthesized and should be subjected to biological screening in a program designed to uncover new and effective sustained-release injectable contraceptives. They also proposed 15 laboratories as candidates for participating in the program to synthesize new steroids. These laboratories, most of which are located in developing countries, were contacted by WHO headquarters staff to determine whether they would be receptive to the idea of participating in the program. The arrangement proposed was that WHO, in addition to supplying literature, material, and chemicals, would fund each laboratory to the extent of $10,000 to $15,000, the sole requirement being that 5 gram quantities of pure steroid would have to be delivered to WHO headquarters. Patent rights would remain with WHO.

Chemical Objectives

The objective of the chemical synthesis program was to modify chemically an active contraceptive steroid drug into a "prodrug" that would either be inactive or less active than the parent steroid. A simple and efficient way to achieve this goal is to protect the free 17-hydroxyl group of an active steroid by inserting an appropriate acid chain, thus producing the corresponding 17-ester (prodrug). When administered to humans, such a prodrug is converted into an active contraceptive agent by enzymatic hydrolysis in vivo (*5*). The rate at which the hydrolysis occurs determines whether the prodrug might be suitable for use as a long-acting, injectable contraceptive. The main goal of the program initiated in 1976 was to design novel steroid esters that could serve to enlarge the number of long-acting injectable contraceptives available to women. The strategy was typical of that used frequently in industrial organizations in that it involved the initial preparation of a number of esters of the known contraceptive agents 17α-hydroxyprogesterone, norethisterone [norethynylestosterone (NET)], and levo-norgestrel. The 17-hydroxyl esters to be investigated has now been expanded to well over 250 compounds.

The natural male sex hormone, testosterone, was also included in the program, since esterification of its free 17-hydroxyl group might afford potential candidates for an injectable male contraceptive. NET was selected as a potential progestin, since laboratory and clinical experience has shown that it is one of the safest progestogens available and is no longer protected by patents. Levo-norgestrel, although still covered by patents, was chosen because of its high progrestational potency. It is thus a good candidate for conversion into long-acting derivatives by esterification.

Organizational Aspects

Eventually, 12 laboratories agreed to participate in the program. The laboratories are located in Australia, Brazil, Bulgaria, German Democratic Republic, Iran, Mexico, Nigeria, Poland, Singapore, Spain, and Sri Lanka (*6*). The participants each received a list of 16 to 20 ester structures, and were invited to submit a research proposal outlining how they intended to synthesize the acid chain to be incorporated into the steroid molecule. They were also asked to submit a budget. Both items were reviewed by the WHO Secretariat with the aid of at least one outside referee and the coordinator of the program (*7*). Once the proposals were approved, a CTS agreement (*8*) was drafted which permitted funding to be instituted.

During the first 3 years of the program the coordinator visited most laboratories at least once. The purpose of the site visits was to brief the investigators about the precise objectives of the program and operating details, to offer appropriate scientific information and advice, to become familiar with the local research facilities, and to solve a number of administrative problems. Each center had different difficulties, for example, inexperienced personnel, lack of sophisticated equipment and instruments, inclement weather conditions, or frequent power failures. Most centers faced one common problem, namely, that of complying with the stringent time and time-consuming regulations that many of the countries impose on importers of chemical reagents and small equipment items. It soon became evident that many of the developing countries would do well to overhaul their customs regulations if they wish to upgrade and expedite scientific research. The only feasible solution for the chemical synthesis program proved to be for WHO to keep in Geneva part of the money allocated to each center. The WHO Secretariat ordered directly the chemicals for the principal investigators in accordance with their requests and budgets, and arrangements were made to ship the chemicals through the auspices of international diplomatic couriers. The organization of such a network is difficult, but in the long range it proved to be crucial because it saved a great deal of time and unnecessary delays and frustrations.

In addition to providing background information and technical literature to all principal investigators, the coordinator was in charge of examining and labeling the samples (a code number was used for every compound submitted by the centers) and checking the data sheets (each sample sent to WHO headquarters was accompanied by a data sheet giving a full description of the substance including its physical, spectroscopic, and analytical properties). The coordinator acted as a general troubleshooter and was easily available to the various principal investigators; together with the WHO Secretariat he reviewed all the manuscripts originating in the various centers because of their possible impact on the filing of patents on behalf of WHO for the most promising compounds.

The preparation of the long-acting esters presented several difficulties. First, the acid chains—encompassing over 100 different chemical structures—had to be synthesized, since most of them had not been described in the chemical literature. Their synthesis invariably involved a number of steps, frequently with a variety of stereochemical problems. Another problem was the esterification reaction, which is difficult to perform on tertiary alcohols of the type present in NET and levo-norgestrel. In several instances, sophisticated techniques were used and each certain acids a new esterification method had to be developed. A third problem, both time- and material-consuming, was that of reaching the requested high purity (about 99 percent).

Formulation and Bioassay

After they were synthesized, all compounds were shipped to the Department of Chemistry of the City University, London, for quality control and further purification, when necessary. The compounds were then forwarded to the School of Pharmacy of the University of London for formulation. Once satisfactory stability was established, sterile crystalline suspensions were sent for bioassay to the National Institute of Child Health and Human Development (NICHHD) of the U.S. Department of Health, Education, and Welfare in Bethesda. This NIH unit under G. Bialy handled both the funding and operational details of the biological evaluation (rodents (and currently in primates). Esters not suitable for the preparation of aqueous suspensions were bioassayed as oily solutions. After leaving WHO headquarters for quality control at the City University, London, every sample was followed by the WHO Secretariat and by the coordinator (appropriate forms were used at every stage of the program) until the biological results were returned.

The bioassay chosen for the determination of the duration of action of long-acting progestogens was the suppression of estrus in female rats, with depot-medroxyprogesterone acetate and norethisterone enanthate—the only two currently available long-acting injectable contraceptives—being used as comparison standards. Tests for prolonged androgenic activity were carried out in castrated male rats, with the weight increase of the ventral prostate being used as the measure of biological activity and testosterone enanthate being used as a standard. The biological results were supplied to the various principal investigators, who frequently undertook the synthesis of additional esters based on particularly promising biological leads.

Present Status

The synthesis and screening programs were reviewed in depth during consultations held in November 1977 (Geneva), January 1979 (Geneva), and January 1980 (Jena, German Democratic Republic) with participation of principal investigators, expert chemists, biologists, the coordinator, and WHO staff members. Approximately 220 steroids had been synthesized in the 12 participating laboratories, many of which had had no previous steroid experience but which are now able and willing to extend such work. The biological evaluation of potential male contraceptives is being discontinued for financial reasons (*9*), but six compounds of possible use in female contraception have now been selected for further development. The next phase of research—testing in primates and preparation of larger amounts for toxicology and for eventual phase I clinical studies in one of the WHO Clinical Centers—has already been initiated. Until now all of this work has been performed outside the regular pharmaceutical industrial channels. If a promising drug should emerge from such phase I clinical studies, then it is anticipated that the large-scale synthesis would be commissioned with some chemical firm before long-term toxicological and phase II and III clinical studies are conducted.

Excluding efforts by military establishments (*10*), this is probably the first instance in which an international public sector agency has launched successfully a program of this nature, and it is reasonable to ask how economical the program is. In terms of time, the chemical synthesis has taken longer than it would have in the steroid synthesis laboratory

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National Institutes of Health (NIH), and the WHO. Also, whereas in the 1960s the overwhelming majority of American obstetricians and gynecologists were men, more than half of the residents and young practitioners in that subdiscipline are now women.

Yet just as women have entered every aspect of contraceptive development—from research and testing to delivery of the product—their choices are becoming more limited. This is primarily a consequence, again, of public, governmental and media response to the complaints in the 1960s and 1970s of women who wanted a perfectly "safe" pill or other contraceptive. What do the professionals ask in contraceptive research have to offer in that regard?

The Current Climate

The fashionable area of human reproductive biology is now the study of infertility rather than contraception. The latest prestige of the latter field is reflected by the paucity of new entrants to it. This is partly because relatively less money is now dedicated to contraception R&D than was the case 15 years ago (30). Not only have industrial expenditures virtually ceased, but the principal U.S. government funding agencies, the NIH and the Agency for International Development, because of mandates initiated under the Reagan Administration, are prevented from supporting many important areas of contraception research. To convert promising laboratory discoveries in animal reproduction into viable methods of human birth control is now so time-consuming, and so dependent on the participation of the pharmaceutical industry, that many scientists have turned to other fields because of the lack of material and societal support.

Another reason that scientific attention has turned away from contraception research is that, since the late 1960s, country after country in the developing world has recognized the problem of uncontrolled population growth and has started to implement birth control programs—some of them, such as the one in China, on a huge scale. Health professionals dealing with the delivery rather than the creation of contraceptive methods then developed that the emphasis in these countries should be placed on education, on the creation of the appropriate infrastructure, on the integration of contraception with maternal and child health care, and on the optimum use of existing methods (the pill, IUD, condom, injectable steroids, and sterilization) rather than on the search for new contraceptive methods.

This focus of Third World governments suggests how different is the perspective of women in the United States compared with that of women in poor countries. Here, IUDs have been rejected by many women, largely because of the defective Dalkon Shield. Makers of other IUDs—the Ortho Pharmaceutical Company with the original Lippes loop and G. D. Searle with the Copper Seven—have also withdrawn them without any pressure from the FDA. IUDs never did play a role, in fact, in the single most important birth control issue in the United States, teenage pregnancy, because the device is unsuited to young, nulliparous women. Yet in China at least 35 million women are estimated (11) to be wearing an IUD developed in the 1960s, thus making it the most prevalent contraceptive in that country. In Mexico, similarly, where the government switched in 1974 from a laissez-faire pronatalist policy to an increasingly aggressive population control program, steroid contraceptives and IUDs are the key components of that program (12), followed by abortion.

In some Latin American countries, such as Brazil, IUDs are hardly used, and the pill continues to be the method of choice (13),

whereas many Asian women prefer steroid injectables (13), while certain women's health groups in the United States continue to oppose. All this proves that couples all over the world need more choices. Strangely, three countries—the Soviet Union, Japan, and the United States—that might be leaders in the process suffer from a pronounced stagnation in the range of choices and the quality of birth control. Many people ignore the fact that incidence of abortion reflects the state of contraception. In the Soviet Union, the country with the highest per capita abortion rate in the world (14), the quality of the contraceptive supply is extraordinarily poor and the pill is essentially unavailable. Japan, the country with the third or fourth highest abortion rate, is the only industrialized country in which the pill is still not approved for contraceptive use (15). The United States, finally, has the highest teenage pregnancy and teenage abortion rate of any industrialized country (16).

I cite these three examples to show that improvements in contraceptive "hardware," in addition to contraceptive "software" (for example, education, distribution, and health care), are likely to have an important effect on rich as well as poor countries. And this brings us back to the intuitive desire of most people in the United States for improved contraception. So what, again, do the professionals have to offer?

Prognosis for New Developments

The 1982 OTA report *Future Fertility Planning Technologies* (21) introduces a list of future contraceptive methods by saying that "between now and the end of this century, more than 20 new or significantly improved technologies for contraception are expected to become available" (21, p. 92). A similar article, published in 1986 under the title *The Next Contraceptive Revolution* (37), gives virtually the same list and cites a lack of financial support as the chief obstacle to its immediate realization.

My own view (38, 39) is much more pessimistic: regardless of the amount of money available, none of the truly revolutionary developments such as antifertility vaccines or a male pill have a chance of being used by the public in this century. The rest of the cited (37) contraceptive improvements, which include another vaginal spermicidal tablet, another copper IUD, and a cervical cap, although clearly useful in a public health and demographic context, are not new or revolutionary. A delivery system for steroid contraceptives, which replaces the daily ingestion of a tablet by steroid-loaded vaginal rings or subdermal implants, is no consolation to women wishing to abandon continuous exposure to a potent steroid hormone, especially when they learn that these supposed novel developments have been under way for nearly 20 years.

A Priority List of New Contraceptive Methods

What new contraceptive methods are needed and who would their principal beneficiaries be? The following list is short, yet ambitious, and arranged in an order of priority that I will justify:

1) *A new spermicide with antiviral properties.* The AIDS epidemic alone justifies putting this item on top of the list. Demonstrating antiviral activity, however, is not sufficient. A drug or formulation needs to be devised that will be effective under conditions of normal sexual intercourse. The noncontraceptive benefit is likely to weigh heavily in any risk assessment and an FDA approval.

2) *A "once-a-month" pill effective as a menses-inducer.* Such a pill would have to be suitable for self-administration, in which case it could become the single most effective method for reducing the 40 to 50 million abortions performed annually throughout the world. In 1970 (11) I outlined the technical steps required to create such an agent and suggested why up to 17 years (the present lifetime of a U.S. patent) would be required for such work. An expenditure of $100 to $150 million now seems a conservative estimate for such a project.

Instead of the current pill, which is taken daily for most of all of each month, the menses-inducing pill would be taken by a woman only during those months when she had unprotected coitus. Theoretically, she would have to take only a single pill (containing a fairly short-lived and rapidly metabolized drug) on the day she expected her next menses. Instead of waiting to see whether she had missed her period, a woman would take the pill on the menstrual flow on the expected time. Such a method would not be acceptable or suitable for every woman, but to many such a one-pill regimen would represent an enormous improvement: at a maximum, a woman would be taking 12 pills annually, rather than the present 250 or more. With such a menses-inducer, women would not necessarily know whether they carried a fertilized egg. The single most important advantage of such a method is that the decision to contracept is made prospectively.

Scientifically, there is little reason to doubt that such an agent could be created. The steroidal antiprogestin mifepristone (RU-486), developed by research workers at Roussel-Uclaf in collaboration with an academic team headed by E. E. Baulieu (40), is the most significant research achievement of the 1980s in new practical fertility control. Current clinical data (41) show that the drug's effectiveness, especially when administered with a prostaglandin (42), is limited to terminating menstrual flow only 4 to 8 weeks after onset of the last menses; its administration mimics, a spontaneous miscarriage. Because RU-486 is likely to disturb subsequent periods (43), induction of regular menses is probably not feasible with this particular drug. Anti-abortionists might benefit from a method like RU-486 the "French death pill" and then threatened boycotts and other actions receiving front-page treatment in the *New York Times* (44) and other newspapers. The support that the Administration and some in Congress gave to these protesters is an indication of the present climate of fertility control in the United States. Neither Roussel Uclaf nor a U.S. pharmaceutical company has so far applied for FDA approval of RU-486, even though hundreds of thousands of women in the United States might benefit from it.

3) *A reliable ovulation predictor.* For couples practicing "natural family planning" who are interested in more precise indicators of a "safe" interval than "natural" methods available now can give, it is much easier to detect (45) the time when ovulation has occurred (that is, the second half of the menstrual cycle) than to predict accurately the onset of ovulation. As human sperm has a fertile life span in the women's reproductive tract of up to 3 days, couples wishing to have unprotected intercourse during the first half of the menstrual cycle need to be able to predict the onset of ovulation by approximately 3 days beforehand. Such precise prediction is now technically feasible. What still remains to be done is to convert this into a financially realistic and operationally practical method for routine birth control. This approach to contraception would be equally attractive to prochoice and anti-abortionist groups. There is an additional educational bonus: for couples to depend on such a method, they would have to understand the timing of ovulation another detail of the menstrual cycle—information that I believe is widely lacking at present.

4) *Easily reversible and reliable male sterilization.* Millions of men especially in the Northern Hemisphere, now undergo vasectomies, a sterilization procedure that is simpler and safer than tubal ligation in females. The overwhelming majority of these vasectomized men already fathers, vasectomy would have to be guaranteed as reversible before young men without children would opt for such a method of fertility control. The reversibility would have to be relatively simple and cheap. At present, vasectomy can only be reversed through expensive microsurgery (46). Even when normal sperm counts are restored, immunological reactions frequently lead to infertile sperm. In the absence of virtually guaranteed restoration of fertility, pre sumably on the basis of epidemiological studies covering a number of years, the prospects for widespread deployment of reversible vasectomy reversals are small, whereas the opportunities for mal practice litigation seem limitless.

5) *A male contraceptive pill.* I give this alternative a lower priority only because of its long development time. In 1970, I documented (11) the technical reasons why developing a male pill would take longer—probably on the order of 20 years—than work on a new female pill, such as a menses-inducer. Long-term assurance of safety that has been attained on by women for the female pill, is only available through large, long-term epidemiological studies. Safety may be more difficult to establish for men than for women, primarily because of the longer fertile lifetime of men.

6) *Antifertility vaccine.* In principle, this would be the most revolutionary development; it would radically change our perception of human fertility if teenage males or females, or both, were vaccinated so that they would be infertile until a conscious step was taken to achieve fertility. To accomplish prompt reestablishment of fertility, a method would be needed that actively reversed the immunological infertility—before vaccination wore off with time. A search for such a method with a focus on the development of antibodies to the female hormone chorionic gonadotropin has been under way for well over a decade (47). Even if the medium-term technical problems are resolved, it will take many years of carefully controlled studies with large numbers of women volunteers to determine how long it takes for the effect of the antifertility vaccine to wear off, whether all women are then able to produce normal babies, and whether there are serious side effects after extensive use of such vaccines.

Current Barriers to Contraceptive R&D

If only these six projects, and no others, were completed successfully, the choice for human fertility control would be vastly expanded for all constituencies—poor and affluent, prochoice and anti-abortion, female and male. What are the chances that this can be accomplished? The following analysis is presented primarily from a U.S. perspective, but it has global ramifications. The complexities of developing any modern drug—contraceptive or therapeutic—restrict such endeavors for all practical purposes to the United States, Japan, a handful of Western industrialized countries, and perhaps eventually China and India. But at present the United States still has an overpowering influence, partly because it represents such an important market.

Two of the six agenda items—a new antiviral spermicide and a

Ingrid Schneider
Ulrike Schaz

ANTI- PREGNANCY- VACCINES

Contraceptive researchers and population planners all over the world dream of "a perfect method", which controls population growth by controlling women and their fertility with medical-technical interventions. Contraceptive vaccines are supposed to be such a "perfect method". According to the announcements of the researchers, birth-control vaccines should be easy to administer, cheap, safe, effective and long-lasting.

Research in immunological methods of birth control has been financed and coordinated from a very early stage onwards: In 1974, the WHO founded the "Task Force on Vaccines for Fertility Regulation" as subunit of the HRP (WHO Special Programme of Research, Development and Research Training in Human Reproduction). This is due to the fact, that private companies widely dropped out of contraceptive research because of rising liability costs.

The most progressive approach is the development of a vaccine against the human pregnancy hormone hCG (human chorionic gonadothropin). The way it works is based on the principle of auto-immunity: The immunological system of a woman's body should be "trained" to react against the hCG-hormone - which is produced by the early embryo a few days after conception - like it reacts to a virus or a bacteria-infection. The mode of action consists of playing a trick on the woman's normal tolerance to hCG by combining the hCG-hormone with vaccines against deseases e.g.tetanus or diphteria. So the woman produces antibodies not only against tetanus e.g. but also against hcg. Implantation of the fertilized egg is inhibited, so the further development of pregnany is stopped: the woman menstruates.

Several research groups all over the world are working to develop immunological methods for controlling fertility. The most advanced scientific group concerned with antifertility vaccines is a team led by Prof. G.P. Talwar, director of the National Institute of Immunology (NII) in New Delhi. Talwar's research budget for anti-hCG-vaccines is sponsored by the Indian Department of Biotechnology in the Ministry of Science and Technology, the Population Council, USA, the Rockefeller Foundation, USA, and the Canadian IDRC. The development of birth control vaccines has top-priority for the Indian government. India plans to introduce these vaccines as part of their so-called family welfare programmes in the mid-90s.

The most competitive team to Talwar's approach is a research team formed by Vernon Stevens, Ohio State University, USA, and Warren Jones, Flinders Medical Center, Australia. This research

team investigates under the umbrella of the WHO-HRP-Programme. Their type of birth control vaccine is also directed to the hCG-hormone. But the vaccine they develop is using a smaller part of the hCG-molecule. Whereas Talwar is using the whole beta-chain of the hCG-molecule, coupled with the alpha subunit of ovine luteinizing hormone (α- oLH) and linked to tetanus or diphteria toxoid as carrier molecule, the WHO-team uses only the carboxy- terminal peptide of beta-hCG, linked with diphteria-toxoid as carrier.

The WHO-team regards Talwar's vaccine as dangerous because it cross-reacts with the hormone LH, necessary for the maintenance of the menstrual cycle. Serious hormonal disorders could occure. The linkage between a mixture of tetanus and diphteria-toxoids is doubtful because allergical reactions are likely to appear, too.

On the other hand, the "disadvantage" of the WHO-vaccine is a much shorter period over which it is effective. While Talwar's vaccine is supposed to last for one year, the WHO-vaccine works a maximum of 6 months. Talwar doubts that the WHO-vaccine elicits enough antibodies to block the hCG effectively and thus stopping pregnancy.
The WHO-team is now planning not to administer the vaccine as an injection but as an implant - putting the components of the vaccine into so-called "biodegradable" plastics. These implants are meant to release the vaccine over a longer period (one year or more after implantation).

HUMAN TRIALS - WOMEN AS GUINEA PIGS

Before a new contraceptive is admitted by the national drug authorities, a long phase of animal experiments and human trials is demanded. The hCG-vaccine was tested in mice, guinea-pigs, monkeys [illegible], and baboons.
The phase I human trials are done to prove the safety of the vaccine and to find out the dosis and mixture of the vaccines. Therefore it is carried out on surgically sterilized women.

Talwar's team performed his phase I trials from 1974 to 1978 on 63 women in India, Finland, Sweden, Chili and Brazil, supported by the International Committee for Contraceptive Research of the Population Council, New York. In this phase I-trial they found wide variations in the amount of antibodies produced and little vaccine response in one quarter of the tested women. Talwar, in a hurry to beat his competitors, in 1976 also tested this former prototype vaccine without permission on six unsterilized women, two of them became pregnant.
Afterwards Talwar employed a new mixture of the vaccine and initiated another phase I of clinical trials in 1986 at five centres in India on 105 women.
Talwar's team claims the vaccine to be devoid of side-effects, only some women having shown "mild hypersensitivity reactions".

The WHO-team carried out the phase I clinical trials on 30 women in Australia. According to the scientists it was free of

side effects and produced "contraceptive levels of antibodies". The pharmaceutical firm Sandoz from Switzerland financially supported these tests.

Phase II clinical trials are expected to show the contraceptive efficacy (whether it really works to stop pregnancy).
Talwar's team initiated phase II trials in May 1990 at three centres in India. The phase II shall be conducted on 180 women. Preconditions for becoming part of the trials are "proven fertility and an active sexual life". The women already have to have two children – because of possible irreversibility of the vaccine.
Those women participating at the trials get three injections of the vaccine, the intervals between these injections being six weeks. The first injection is a mixture of beta-hCG conjugated to tetanus as well as diphteria, followed by one of diphteria and one of tetanus. The women undergoing the trial have to give a blood sample every two weeks. These samples are checked at the NII. If the antibody levels are considered to be too low they receive a booster injection (beta-hCG conjugated to diphteria or tetanus alternatively).
For the targeted mass production of the vaccine its genetically engineered production is in progress.

Until now, the WHO-team has not yet started phase II trials of their anti-hCG-vaccine.

MEDICAL CRITIQUE

So far side effects and long-term-effects are unpredictable. It is entirely unknown whether the hCG-vaccine blocks hCG only or whether it blocks other body functions, too. Severe health hazards for the endocrinological and immunological system are possible.

The linkage of hCG to other vaccines like tetanus or diphteria toxoid as carrier-molecules can cause allergical reactions and immunological disorders. Especially the "vaccine-cocktails" Talwar is using runs potential health risks. Auto-immune-diseases could occure.

The amount of antibodies sufficient for safe contraceptive effect is not yet known. One single injection is not even lasting for half a year or one year: After the first three injections booster injections are necessary. But how can a woman know if she has still got enough antibodies circulating in her blood? Therefore the WHO intents to develop a diagnostic kid (antibody-measuring blood-test) for self-use. But this surely will be no easy and cheap technique.

Women's reactions towards the hCG vaccine show a great variety of antibody levels. The duration of the vaccine's effect will differ individually and can't be predicted precisely. What's the use of a contraceptive method, when the woman doesn't know whether it still works???

In addition, the hCG-vaccine has a so-called lag-period before it is effective. Talwar's vaccine doesn't work effectively until three months after the first injection. For this period of time, contraception with another non-hormonal-method (IUD e.g.) is needed.

Nobody knows what will happen, if a woman who becomes vaccinated is pregnant or gets pregnant within the first three months after the injection; the anti-hCG-vaccine may work as an abortifacient or the development of the fetus could be very negatively affected.

When the effect of the vaccine drops - which the researchers consider to happen not abruptly but slowly - the problem is the same: a "safe", non-hormonal contraceptive method has to be used. Possible interactions between the anti-hCG-vaccine and hormonal contraceptives like the pill, injections etc. are not yet investigated, but are feared.

On the other hand, the vaccine is at least temporarily irreversible. It cannot be "switched off" for the duration of it's effect nor can it be reversed - even if severe health disorders occure.

It`s not sure if the effect of the anti-hCG-vaccine can be totally reversed at all. It's also possible that the vaccine has to be regarded as a sterilization method. Even very small amounts of antibodies remaining in the woman's body could lead to permanent infertility.

According to the considerations of WHO the effect of the vaccine on women with specific immune status due to e.g. malnutrition, parasitic diseases or HIV infection should be taken into account. But in the group targeted with the vaccination - poor women in Third world- countries - malnutrition and weakness of the immunological system can be taken for granted! The immunological chaos the vaccination might cause in these women is unforeseeable!

All this makes clear that the easyness and safety of administration of the anti-hCG-vaccine which is promoted by the researchers is definitely wrong.

GENERAL CRITIQUE

Besides these points of severe medical doubts there are lots of principal critics against the anti-pregnancy-vaccine:

The mode of action of the anti-hCG-vaccine - based on the coupling with vaccines against deseases like cholera, tetanus, diphteria etc. - offers enormous possibilities for political misuse: Women could get vaccinated without their knowledge or consent. The anti-hCG-vaccine can be easily abused under social circumstances where women can't choose their contraceptive method themselves - like in coercive family planning programmes

or in psychiatric institutions. The vaccine is suitable for compulsary measures.
The birth-control vaccine takes control from woman over their body and their reproductive capacity, similarly to implants and contraceptive injections. It could result in the control of doctors and family planners over women.

Anti-pregnancy-vaccines are provider-dependant: Women need health care services which administer the vaccine. Paradoxically the principle of vaccines is, that it could also be given by mobile teams without integration in general health care services. What happens in such cases if side effects arise?

Contraceptive researchers and population planners generally identify woman's sexuality with fertility. But there are lots of possibilities for woman to experience enjoyable, satisfying sexuality without the danger of pregnancy. This is being ignored by these stupid, techno-orientated men.
Like all modern contraceptives birth-control-vaccines separate radically contraception and fertility from sexuality. There is no need for an agreement on modes of contraception and forms of sexuality between woman and man. Men remain free of taking responsibility for their fathering-capacity and contraceptive issues.

Unlike many researchers and familiy planners want to make us believe, pregnancies are not only the result of contraceptive failures. In many countries children are necessary for sustaining the family and as an old-age-insurance. And they are of emotional and social importance for their parents -e.g. as a support and hope for the future. In many patriarchal societies, only the birth of children (particularly sons) gives women social acknowledgement.
Hence unwanted pregnancies are not only an expression of lacking contraceptive techniques but can also simbolize the social powerlessness and missing autodetermination of women.

Family planning programmes that really strive for the strengthening of women's control over their bodies and their lifes should support women to gain knowledge about their body and their health. They should give women space to exchange their experiences with men and sexuality und to share critics and changes. This would be one step to overcome the hierarchical gender-relations which are also reflected in sexuality, procreation and all the questions concerning children.
Family planning programmes in India and elsewhere have nothing in common with feminist approaches. Even in so-called progressive projects which integrate family planning into mother-child-health programmes, sexuality and sensuous bodyliness are taboos.

Many researchers concerned with anti-pregnancy vaccines describe people and pregnancies as an epidemic: in a cynical way this metaphorical vision interpretes women and their wombs

as a disease. And they declare them to be the target for medical attacks. – We should attack this sexist, antihuman vision!

Many researchers have the dream to give anti-pregnancy vaccines as mass immunizations. This reveals their extremely technocratic , reductionist and sexist attitude. The necessary changes of the social, economical, political, patriarchal structures is not in their focus of interest.

If women don't oppose to their plans, the researchers dream will turn out as a nightmare.

LET'S START A POWERFUL INTERNATIONAL CAMPAIGN AGAINST

THE FURTHER DEVELOPMENT OF THE ANTI-PREGNANCY-VACCINE !!!

In Germany, the BUKO-Pharma-Campaign
(member of the Health Action International – Network)
intents to start a campaign against
the anti-pregnancy-vaccine.

Contact:

BUKO-Pharma-Kampagne
August- Bebel- Str. 62
4800 Bielefeld
F.R. Germany

NATIONAL INSTITUTE OF IMMUNOLOGY, NEW DELHI

PHASE II CLINICAL TRIAL OF ANTI-hCG BIRTH CONTROL VACCINE

SCREENING FORM.

Name of woman _____ Sub No. _____

Address _____

Inclusion Criteria	*Yes*	*No*
1. Healthy informed female volunteer with written consent	☐	☐
2. Age 20-35 years	☐	☐
3. Regular menstrual cycles for last 3 months (22-35 days)	☐	☐
4. Confirmation of ovulation by estimating progesterone level at 18 and 24 day of cycle and supplemented with ultrasonography whenever possible.	☐	☐
5. Exposed to the risk of pregnancy (Cohabitating with husband)	☐	☐
6. Has at least two living children	☐	☐
7. Age of second child more than one year	☐	☐
8. Stabilized on IUD or non hormonal contraceptive (minimum 3 months)	☐	☐
9. Willing to get IUD removed or discontinue contraceptive method after 13-14 weeks	☐	☐
10. Ability to return for follow-up at required interval	☐	☐
11. Able to maintain menstrual diary card	☐	☐
Exclusion Criteria		
12. Suspect pregnancy	☐	☐
13 Currently breast feeding	☐	☐
14. H/O recurrent abortion	☐	☐
15. H/O secondary infertility	☐	☐
16. H/O chronic allergy disorders (Eczema, Hay fever, asthma, skin rash, etc.)	☐	☐
17. Evidence of autoimmune disease (Rheumatiod arthritis.)	☐	☐
18. Evidence of endocrine disorder (Diabetes, Grave's disease, etc.)	☐	☐
19. Known or suspected malignancy of breast or pelvic organs	☐	☐
20. Hypertention (B.P. > 140/90 mm Hg)	☐	☐
21. Hb < 8 gm %	☐	☐
22. Cervical cytology not normal	☐	☐

The subject will be enrolled in the study, If answers to questions 1-11 are yes and answers to questions 12-22 are no.

Name and signature of the

Investigator Date

NATIONAL INSTITUTE OF IMMUNOLOGY, NEW DELHI

PHASE II CLINICAL TRIAL OF ANTI-hCG BIRTH CONTROL VACCINE

ADMISSION FORM

Name of woman _____

Address _____

IDENTIFICATION

1. ICMR Job No. [ ][ ][ ][ ][ ] 1-5
2. Study No. [ ][ ][ ][ ][ ] 6-10
3. Centre [ ] 11
4. Subject No. [ ][ ] 12-13
5. Study group (cut off level of Antibody titre for booster injection) 1. 150 ng/ml 2. 75 ng/ml [ ] 14
6. Age of woman (years) [ ][ ] 15-16
7. Education [ ] 17
   1. Illiterate 2. Read and Write
   3. Primary 4. Middle
   5. High School 6. Above High School

OBSTETRIC HISTORY

8. No. of pregnancies [ ][ ] 18-19
9. No. of live births [ ][ ] 20-21
10. No. of still births [ ] 22
11. No. of spontaneous abortions [ ] 23
12. No. of induced abortions [ ] 24
13. No. of living children [ ] 25
14. Age of second child (months) [ ][ ] 26-27
15. Breast feeding [ ] 28
    1. No 2. Yes
16. Date of last pregnancy termination [ ][ ][ ][ ][ ][ ] 29-34
17. Outcome of last pregnancy [ ] 35
    1. Live birth 2. Still birth
    3. Spontaneous abortion 4. Induced abortion
18. Current contraception [ ] 36
    1. IUD 2. Non Hormonal
19. Duration of last contraceptive used (mths) [ ][ ] 37-38

MEDICAL HISTORY

20. Illness within last 6 months [ ] 39
    01 No
    If yes specify
21. Present complaints [ ] 40
    01 No
    If yes specify
22. Current medication [ ] 41
    01 No
    If yes specify

Menstrual Patern
(last 3 months)

23. Usual cycle length (days) [ ][ ] 42-43
24. Duration of bleeding (days) [ ][ ] 44-45
25. Amount of bleeding [ ] 46
    1. Scanty 2. Moderate 3. Profuse
26. Date of LMP [ ][ ][ ][ ][ ][ ] 47-52

EXAMINATION

27. Systemic examination [ ][ ] 53-54
    01. Normal
    if abnormal specify
28. Breast examination [ ] 55
    1. Normal
    if abnormal specify
29. Blood Pressure (Systolic) [ ][ ] 56-57
30. Blood Pressure (Diastolic) [ ][ ] 58-59
31. Height (Cm) [ ][ ] 60-61
32. Weight (Kg) [ ][ ] 62-63

PELVIC EXAMINATION

33. Vagina [ ] 67
    1. Normal
    If abnormal specify
34. Vaginal discharge [ ] 68
    1. None 2. Pysiological
    3. Pathological

Phase II - Trial

WHH 310

NATIONAL INSTITUTE OF IMMUNOLOGY, NEW DELHI
PHASE II CLINICAL TRIAL OF ANTI-hCG BIRTH CONTROL VACCINE
Follow up Record.

Name of woman _____ Husband _____

Address _____

IDENTIFICATION

Study No. 9001

Centre

Subject No.

Study group
(incl. all level of antibody titre for booster)
1. 150 ug/ml
2. 75 ug/ml

Follow up visit No.

Date of follow -up

Interval since first injection (weeks)

DELAYED REACTION TO LAST INJECTION

Systemic
01 None
If yes specify _____

Local
01 None
If yes specify _____

OTHER COMPLAINTS

9. General
01 None
If yes specify _____

1. Menstrual
01 None
If yes specify _____

GENERAL EXAMINATION

11. Systemic examination
01 Normal
If abnormal specify _____

13. Date of LMP

14. Blood samples for antibody titres
1. Yes 2. No

15. If yes level of antibody titres (ng/ml)

IMMUNIZATION STATUS

16. No. of previous injections

17. Is injections given at this visit
1. No 2. Yes

18. If no, reason _____

19. Constituents of vaccine (200 ug)
1. alpha sb,H.8-hCG/DT+TT
2. alpha sb,H.8-hCG/TT
3. alpha sb,H.8-hCG/DT

REACTION TO SENSITIVITY TEST

20. Systemic
01 Absent
If present specify _____

Local

22. Redness
1. Absent 2. Present

22. Swelling
1. Absent 2. Present

23. Tenderness
1. Absent 2. Present

24. Itching
1. Absent 2. Present

REACTION WITHIN 3 HRS

25 Systemic
01 Absent
If present specify _____

Local

26. Redness
1. Absent 2. Present

27. Swelling
1. Absent 2. Present

28. Tenderness
1. Absent 2. Present

29. Itching
1. Absent 2. Present

30. Any treatment for reaction
01 No
If yes specify _____

STATUS OF CASE

31. Is the subject continuing in the trial
1. No 2. Yes
If no give following details

31. Date of last injection)

33. Total number of injections

34. Date of discontinuation

35. Reason of discontinuation _____

(In case of pregnancy, enclose pregnancy report form)

Name of Investigator

Signature

Date

The following information from item 36 to 47 should be completed every three monthly or earlier if indicated

36. Date of IUD removal/Discontinuation of other contraceptive (Enter 999999 if not removed)

37. Breast examination
1. Normal
If abnormal specify

38. Blood Pressure (Systolic)

39. Blood Pressure (Diastolic)

40. Weight (Kg)

PELVIC EXAMINATION

41. Vagina
1. Normal
If abnormal specify _____

42. Cervix
1. Normal
If abnormal specify _____

UTERUS

43. Size of Uterus
1. Normal 2. Small 3. Large

44. Mobility
1. Free 2. Restricted 3. Fixed

45. Tenderness
1. No 2. Yes

ADNEXA

46. Tenderness
1. No 2. Yes

47. T. O. mass
1. Absent 2. Present

48. Date of next
follow up visit _____

Remarks

34. Cervix
1. Normal
If abnormal specify

UTERUS

36. Position
1. Anteverted 2. Retroverted 3. Mid position

37. Size of Uterus
1. Normal 2. Small 3. Large

38. Mobility
1. Free 2. Restricted 3. Fixed

39. Tenderness
1. No 2. Yes

40. T. O. mass
1. Absent 2. Present

41. IUD in situ
1. Yes 2. No 3. Not applicable

42. Hemoglobin (gm %)

43. Urine examination
1. Albumin 2. Albumin 3. Sugar
1. Albumin + Sugar

44. Cervical cytology
1. Normal
If not normal specify grade

45. Blood samples for antibody titre
1. Yes 2. No

46. Level of antibody titre
(ng/ml)

47. Constituents of vaccine (200 ug)
1. alpha sb,H.8-hCG/DT+TT
2. alpha sb,H.8-hCG/TT
3. alpha sb,H.8-hCG/DT

Reaction to sensitivity test

48. Systemic
01 Absent
If present specify

Local

49. Redness

1. Absent 2. Present

50. Swelling
1. Absent 2. Present

51. Tenderness
1. Absent 2. Present

52. Itching
1. Absent 2. Present

53. Date of first injection

Reaction to injection (within 3 hours)

54. Systemic
01 Absent
If present specify

Local

55. Redness
1. Absent 2. Present

56. Swelling
1. Absent 2. Present

57. Tenderness
1. Absent 2. Present

58. Itching
1. Absent 2. Present

59. Any treatment for reaction
01 No
If yes specify

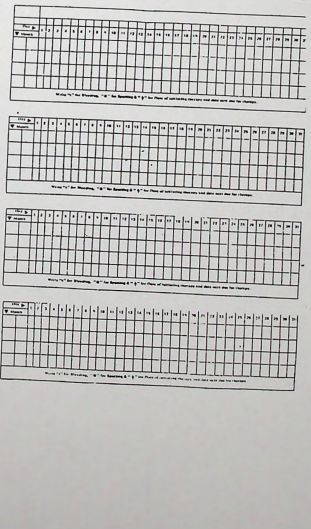
60. Date of next
follow up

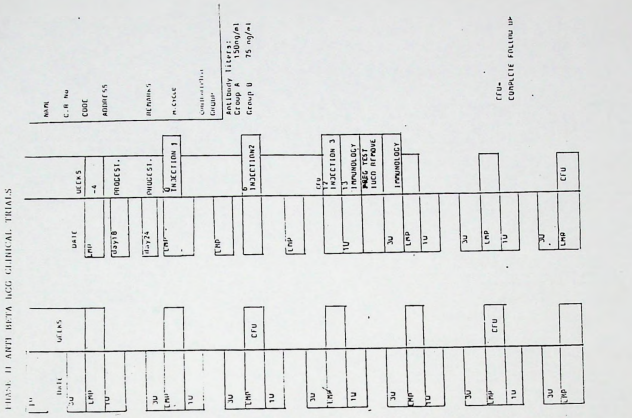
Remarks

Name of Investigator

Signature

Date





NATIONAL INSTITUTE OF IMMUNOLOGY
BLOOD ANALYSIS

SUBJECT DETAILS	HAEMATOLOGICAL RESULTS	CLINICAL CHEMISTRY RESULTS
Study	Haemoglobin.....g%	Alkaline Phorphatase.....I.U./lit.
Centre	Total Leucocyte Counts.....per mm³	Bilirubin.....mg%
Subject Name/Code	Differential Leucocyte Counts	Cholesterol.....mg%
Date of Present Bleed	Neutrophils.....%	Creatinine.....mg%
Date Received	Lymphocytes.....%	Glucose.....mg%
Type of Specimen	Monocytes.....%	SGPT.....I.U./lit.
a) Whole Blood in EDTA for Haematology	Eosinophils.....%	SGOT.....I.U./lit.
b) Serum for Clinical Chemistry	Packed Cell Volume.....%	Urea.....mg%
Date of Testing	Platelet Count.....lakha/mm³	Total Protein.....g%
Investigations Done	ESR.....mm/1st hr. (Wintrobe's method)	Albumin.....g%
a) Haematology		Globulin.....g%
b) Clinical Chemistry		A/G Ratio.....

Signature

National Institute of immunology, New Delhi

Annual report, April 1989 to March 1990

Birth control vaccines

While an animal birth control injection, Talwar is seer to the point of reaching the public through industry, birth control vaccines for regulating human fertility would be highly desirable as additional methods to the present options for family planning. Vaccines are attractive propositions on several grounds. They would require only periodic intake, will be free of 'user failure' risk. A vaccine inducing the formation of antibodies against pregnancy hormone, the human chorionic gonadotropin (hCG) has been described in previous reports. Extended Phase-I clinical trials on two alternate formulations of the vaccines were completed this year in three clinics located at the Postgraduate Institute of Medical Education & Research (PGIMER), Chandigarh, All India Institute of Medical Sciences (AIIMS) and National Institute of Health & Family Welfare (NIH&FW), New Delhi. Based on the results of the trials, formulation A consisting of a heterospecific conjugate (HSD), βhCG associated with heterospecies a subunit of LH, linked to either tetanus toxoid (TT) or diphtheria (DT) has been selected for Phase-II trial. The vaccine used at 300 μg dose generated antibodies above the presumed threshold required to prevent pregnancy. The vaccine is now entering the crucial Phase II studies, whereby its efficacy in women will be ascertained. The effect of the vaccine is so far established in monkeys and baboons. Phase I trials have cleared the safety of the vaccine and its reversibility. The trials would determine if immunization can indeed prevent pregnancy and would also provide information on the threshold titres of antibodies required to do so. The protocol was submitted to the Drugs Controller of India on the

6th January, 1990 for clearance to start the Phase II trials. Approval should come in the next few months.

Another vaccine designed at the Institute induces antibodies against LHRH, a key hormone made in the hypothalamus, an area of the brain, which regulates the production of gametes and sex steroids in both male and female. The vaccine is therefore usable in both sexes. We intend to make use of this vaccine for therapeutic and preventive purposes. A possible therapeutic action of the vaccine was indicated by studies in experimental animals reported last year. Immunization of male rats with the vaccine produced a marked atrophy of the prostate, akin to 'immunological surgery'. Similar effect was also seen in monkeys. Toxicology studies were completed with this vaccine as per the national guidelines and these were approved by the ICMR Expert Committee. Permission was sought from the Drugs Controller of India, and trials were started with the vaccine at the PGIMER and AIIMS after due approvals of the Drugs Controller and the Institutional Ethics Committees. By the end of March 1990, nine patients of carcinoma of the prostate were enrolled at PGIMER and thirteen at AIIMS. Immunization with the vaccine has induced formation of antibodies against LHRH in patients with concomitant fall of LH, FSH and testosterone. Clinical improvement has been reported in some patients. Similar trials with this vaccine in prostate carcinoma patients have started in two centres abroad - at Salzburg, Austria and Santa Domingo, Dominican Republic.

The LHRH vaccine has also the potential of use as a post-partum method for prolonging the lactational amenorrhea and inter-child interval in women. Neonatal toxicology studies were undertaken in monkeys. Mothers were immunized soon after delivery. The effect of immunization on breast feeding and growth of the progeny was observed. Immunization did not influence lactation or nursing behaviour and the weight gain of the progeny was similar to that of the controls. No LHRH antibodies were detectable in the mothers' milk or in infants' blood. These studies have cleared the ground for development of a protocol for studying the utility of the vaccine in post-partum women.

A highly interesting new observation has been made this year on the anti-fertility effects of neem oil given in small amounts in the uterus. Animals become infertile without any observable ill-effects. Normal ovarian function and libido are maintained. The action is brought about by cells mobilised *in situ* by instillation of the oil. The effect is reversible and rats readered infertile regain fertility after 4-6 months. This novel use of a traditional plant product, has the potential of serving as a 'vacation' contraceptive. It will also be extremely useful to cover the time period for appearance of antibodies in women immunized with our birth control vaccines. Preliminary studies also indicate the contraceptive action of neem oil used intra-vaginally in monkeys.

A desirable requirement in birth control vaccines is their ability to generate high antibody titres after a single injection, which could be sustained by a booster for prolonged periods. In quest for a vaccine with this property, a live recombinant vaccine was developed using vaccinia as vector. The gene for βhCG alongwith an anchor sequence was inserted in the virus at a 'non-detrimental' locus. Monkeys immunized with this vaccine produced high titres of antibodies with high affinity for binding to hCG and capacity for neutralizing its bioactivity. The efficacy of immunization with this vaccine for prevention of pregnancy will now be determined as also the reversibility and safety of the procedure.

Gene expression

Successful expression of luciferase has been achieved in baculovirus expression system. The gene has been expressed both in insect cells as well as in insect larvae paving the way for understating the preparation of human proteins of utility in this system. Promising headway has been made for expression of α and βhCG in this system.

Probes

A synthetic probe has been developed, which is specific for the human Y chromosome and characterizes without ambiguity, the male from the female, in small samples of DNA. Two independent, yet complementary approaches of research have led to generation of different probes for use in DNA fingerprinting, paternity testing and identification of individuality. Refinements have been made on the probe for tuberculosis. The tetramer probe for HBV is putting in evidence clinical cases picked up by this probe that are negative to traditional serological markers for hepatitis B. These investigations suggest the existence of hepatitis caused by variants of HBV.

Publications

The work carried out by scientists of the Institute was the subject of 49 publications in recognized journals, monographs and proceedings of symposia. The Institute also applied for eight patents in India, U.K., Canada and U.S.A.

Designations

The Institute continues to be a WHO Collaborating Centre for Research and Training in Immunology for India and the South East Asia. It has also been designated as a centre for UNESCO's 'International Network for Molecular and Cell Biology' and as a centre for the 'Asian Network for Biotechnology Applied in Animal Production and Health' of the FAO. NII is a recognized node of the International Hybridoma Databank.

International collaboration

The Institute has ongoing collaborative programmes with the Institut Pasteur, Paris, Centre for Biomedical Research, the Rockefeller University and the International Committee on Contraception Research of the Population Council, New York. A new US-AID CD & RI grant links projects of the Institute with the Harvard Medical School and the Centres for Disease Control, Atlanta. NII is also involved in collaborative projects with institutions in the USSR under the IUTP programme and with Bulgaria and Hungary under programmes of cooperation in science and technology.

Clinical trials with the counter human chorionic gonadotropin vaccine

G.P.Talwar, Om Singh, Indira Kharat, Rahul Pal, K.Arunan and Subash Sad with clinical collaboration of K. Dhall of the Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, K. Buckshee of the All India Institute of Medical Sciences (AIIMS) and A.K.Banerjee of the National Institute of Health and Family Welfare (NIH&FW), New Delhi.

Human chorionic gonadotropin (hCG) has an important role in implantation and sustenance of early pregnancy. One of the birth control vaccines under development at the Institute has the rationale in the induction of formation of antibodies inactivating hCG. The vaccine employs the entire β subunit of hCG linked to carriers such as tetanus toxoid (TT) and diphtheria toxoid (DT). In an earlier study it was observed that βhCG - TT (formulation B) induced the formation of anti-hCG and anti-TT antibodies in women. However, the response was variable and some women had only low antibody titres. To enhance the antibody response, an adjuvent, SPLPS was added to the first dose of the vaccine. The intrinsic immunogenicity of the vaccine was further raised by employing two other strategies — in one of them βhCG was annealed to heterospecies alpha subunit (noLH) to generate heterospecies dimer (HSD) (Talwar et al., J. Reprod. Immunol. 14, 203-212, 1988). This dimer had a conformation recognized by the target tissue receptors. It did not induce antibodies cross-reactive with hFSH and hTSH. The bioneutralizing capacity of antibodies made by HSD was superior to those induced by βhCG (Pal et al., Am.J.Reprod. Immunol.Microbiol. in press). It was also observed that the mixed formulation of βhCG and βoLH linked to carriers (MI) had higher immunogenicity in monkeys than βhCG alone (Talwar et al. Fertil. Steril. 52, 739-744, 1989). After due toxicology study and approval of Drug Authority and Institutional Ethics Committees, phase I clinical trials were conducted in 101 women to determine the safety and relative immunogenicity of the three formulations. These studies reported in the previous years demonstrated that formulation M had a comparative low immunogenicity than formulation B or HSD (formulation A, henceforth) (Talwar et al. Contraception, 41, 301-316, 1990 and Kharat et al. Contraception, 41, 283-290, 1990). No clear cut conclusions could be made on the relative immunogenicity of B and A formulations. It was also observed that there were a few incidents of hypersensitivity reactions encountered in women who had repeated immunizations with the single carrier based vaccine.

An Extended Phase I study was conducted to determine whether alternating carriers could obviate hypersensitivity reactions. In addition to confirming the findings of the Phase I trials, the Extended Phase I trial was also designed to select the best formulation for phase II efficacy trials.

Thirty six women in the fertile age group (25 - 35 yrs.) who had undergone tubal ligation, were recruited for the study at AIIMS, PGIMER and NIH&FW. They were administered 33 μg, 100 μg or 300 μg dose of either βhCG-TT/DT or noLH βhCG-TT/DT formulation. The first injection had TT as carrier, second and third injections had DT as carrier and the fourth injection again had TT as carrier. Six control subjects were concurrently administered the vehicle alone. Two cycles of each subject were studied for basal volume prior to immunization. The clinical chemistry and hematological parameters were recorded at six-monthly intervals and clinical examination was conducted every 4 to 8 weeks. None of the vaccine recipients demonstrated hypersensitivity reactions following the revised schedule of alternate carriers, thus demonstrating the advantage of the 'alternate carriers approach'.

Menstrual cycles were grouped into normal (22-35 days), short (< 22 days) and long (> 35 days) categories based on cycle-length. In recipients of formulation A, 83.5% cycles were of normal duration, 8% were of shorter duration and 8.5% of longer duration. The corresponding figures in the recipients of formulation B were 83.6%, 8.2% and 8.2% respectively, and in control subjects, 82.6%, 7.3% and 10.1% respectively.

Sex steroid glucuronides in the urine of subjects were determined, one cycle prior to immunization and two cycles during the phase of circulating antibody titres. Pregnanediol-3-glucuronide (PDG) levels in all urine samples analyzed indicated that the cycles were ovulatory. Adequate corpus luteal function was evident, but in some cases the area under the PDG curve was decreased.

Anti-hCG response

Every recipient of the vaccine generated anti-hCG antibodies. The peak titres ranged from 222 to 6085 ng hCG binding capacity /ml of serum with formulation A and 120 to 3250 ng/ml with formulation B. The peak values were attained after the third injection. Response to a booster injection given at 6 - 8 months was observed in all but 4 subjects. A dose related response was not obvious amongst recipients of formulation B. However, a dose response was evident for formulation A, with the highest antibody levels being generated at 300 µg dosage. The mean duration of antibody titres >20 ng/ml which is presumed to be the protective level on theoretical grounds based on reported hCG levels in early pregnancy, was 11 months in recipients of formulation B and 12 months in formulation A recipients. Antibody titres >150 ng/ml persisted for 7 months in women receiving formulation A, in contrast to 4.5 months for B.

Formulation A dose (µg)	Duration of Antibody titres (in months)		
	>20ng	>75ng	>150ng
B-300	11	7.5	4.5
A-300	12	9.0	7.0

The antisera showing peak anti-hCG titres were analyzed for cross-reactivity with hLH, hFSH & hTSH. No cross reaction was observed with hFSH or hTSH in any case. Cross-reactivity to a varying degree (15 - 75%) was observed with hLH. Antibodies had a high affinity for hCG, the association constant was K_a= 10^9 to 10^{11} M^{-1}. The bioactivity of anti-hCG antibodies was assessed in a Leydig cell competitive inhibition assay. Antibodies prevented hCG-stimulated testosterone production. Binding of radiolabeled hCG to Leydig cell receptors was also inhibited by the antisera.

Challenge tests

Immunized women were administered increasing dose of exogenous hCG (500, 1000, 1500, 3000, 6000, 10000, and 15000 IUs of hCG) from day 9 post-LH surge. Morning urine of subjects undergoing the challenge test were analyzed for bCG. Serum progesterone levels were also monitored. It was observed that no bCG immunoreactivity was detectable in the urine of women who had high anti-hCG antibody titres (>300 ng/ml). Serum progesterone levels declined progressively till the sixth hCG injection. Vaccinees with moderate anti-hCG titres had no bCG in their urine upto day 4 post-hCG challenge and vaccinees who had titres of <50 ng/ml anti-hCG antibodies, had detectable levels of bCG in urine after two days of hCG challenge. These results seem to indicate that the antibodies have the capacity to neutralize exogenous hCG and prevent sustained progesterone synthesis by the luteal cells, and the amount of hCG inactivated varied with the prevailing titres.

Results of these trials also indicate that formulation A was the more immunogenic of the two. The latency period between the start of immunization and the appearance of antibodies was shorter with formulation A. Amongst the three doses investigated, 300 µg dose of the A formulation gave the highest titres. Based on these observations, formulation A at 300 µg was selected for Phase II efficacy studies. Protocol for the phase II studies was submitted to the Drugs Controller of India for approval. The trials are expected to commence in May, 1990.

Teratology studies on hCG vaccines

M.G. Sharma and S. Jayaraman in collaboration with P.L.Sharma of the PGIMER, Chandigarh.

Teratological studies with the bCG vaccine were carried out in rats following the guidelines of the Indian Council of Medical Research (ICMR) by Prof. P.L.Sharma, Department of Pharmacology, Postgraduate Institute of Medical Education and Research, Chandigarh. The protocol envisaged the administration of the vaccine to female animals to determine any possible interference in the embryonic and fetal development induced by the bCG vaccine. Simultaneous studies were carried out in rats treated with Aspirin/Acetaminophen, to serve as positive controls. The studies indicate that the bCG vaccine is safe and does not cause any developmental (both visceral and skeletal) abnormalities when administered to pregnant animals.

Long-term studies have also been conducted in monkeys and baboons immunized with the hCG vaccine. In every case, the antibody response was reversible. With declining antibodies, the animals resume fertility - 12 baboons and 64 bonnet monkeys remained pregnant under these conditions, had normal deliveries at term and produced normal healthy infants. The growth and development of these infants were monitored anthropometric measurements and developmental land marks. The infants were kept under observation till they attained maturity and two of these have also delivered normal healthy second generation infants.

Recombinant hCG vaccine

I. Srinivasan, L.Lall, Om Singh, Rahul Pal, S.Chakrabarti and G.P. Talwar

A recombinant vaccinia virus carrying the gene for βhCG along with a membrane anchor sequence of 49 amino acids was constructed. βhCG-expressed alongwith the transmembrane segment gets localized on the membrane of the infected cell is seen by immunofluorescence probes. Immunogenicity studies were carried out in two groups of 6 WISTAR rats at different doses of the recombinant virus. A dose dependent antibody response was observed. At 10^7 pfu, all animals made antibodies after a single immunization and the titres were sustained for seven months.

Studies were expanded to bonnet monkeys. The animals were given the anchored βhCG vaccinia recombinant (VSS2). Primary immunization followed by a booster with vaccinia and/or with the peptides generated extremely high titres of anti-hCG antibodies. The antibodies had a high association constant. K_a=10^{10-11} M^{-1}. The antibodies were also potent to inhibit the binding of the hormone to the receptor. Fertility studies are in progress to determine the efficacy of the vaccine for control of fertility in bonnet monkeys.

Expression of a chimaeric βhCG-HBsAg fusion protein in mammalian cells

Anil Mushrik, P.S.Khandekar and G.P.Talwar in collaboration with I.W. Lorrick of Cirss corporation, USA

Construction of a chimaeric gene by fusion of βhCG cDNA and HBsAg was described earlier. This fusion cassette was cloned in two mammalian expression vectors, placing it downstream of either SV40 early promoter or the human β actin gene promoter. The two constructs were transiently transfected into mouse LMtk⁻ cells and their expression levels compared. It was observed that the expression levels of the human β actin construct was two-fold of that obtained with the SV40 construct. Different mammalian cell-lines to express βhCG, were explored. CHO cell-line was established as the most efficient. Stable clones obtained from one of the constructs were characterised in detail using Southern blots. Results indicate that the fusion cassette had undergone on further recombination. Studies on the expression of the cloned gene products is in progress.

Expression of α and βhCG in insect cells using baculovirus expression vector

Bita Nakhai and Sayed E.Hasnain

To enable the cloning of bCG at the Bam HI site of baculovirus transfer vector, Hind III fragments of α and βbCG were provided. Bgl II linkers and independently cloned into the Hind III site of pUC18. The two genes were excised out as Bgl II fragments and cloned into a baculovirus transfer vector. The recombinant plasmids pAcαbCG and pAcβbCG were characterized by restriction analyses and sequencing to verify the orientation of the insert with respect to the polyhedrin promoter. Caesium chloride purified recombinant plasmids were used to cotransfect *Spodoptera frugiperda* (Sf9) cells alongwith wild type AcNPV DNA. The extracellular virus particles were serially diluted and used for seeding Sf9 cells. Recombinant plaques were isolated and purified using a series of plaque assays. The βbCG recombinant virus is being amplified and will be used to infect Sf9 cells. Recombinant βbCG will subsequently be quantitated in an RIA.

The purified αbCG recombinant was used to infect Sf-9 cells and the infected cell supernate was aliquoted at 48, 60 and 72 hrs after infection. The expression levels were quantitated by RIA. Maximal amounts of hCG (10 - 12 µg/ $2x10^6$ cells) was produced at 72 hrs post-infection. A significant amount of the hCG was not secreted but remained within the cell as revealed by ^{35}S-methionine labeling. The recombinant bCG was able to combine with purified βbCG to form functional hCG. This semi-recombinant hormone could compete with ^{125}I-labeled hCG in binding to the CG receptor in rat testes and could also stimulate the production of testosterone in a mouse Leydig cell assay.

In order to enhance the expression level of αbCG, a translational amplification was made by constructing a recombinant pAcαbCG-αbCG virus and which had a trimer of αbCG ligated in tandem in the correct orientation. This was used to cotransfect Sf9 cells alongwith AcNPV DNA and purified vAcα-T virus was obtained. The expression levels of αbCG by vAc αbCG and vAcα-T are being quantitated for comparison.

Molecular cloning of placenta-specific antigens

Rajinder Kaur and S.K. Jain

Construction of a human placenta cDNA library and isolation of a clone using monoclonal antibodies generated against the placenta-specific heat-stable alkaline phosphatase (HSAP) were described in the previous report. The clone was further characterized and was observed to be of about 2.3 kb size synthesizing a 43 kD protein. This protein has biological activity. Similar clones were also picked up from a term placenta library and are being characterized.

A monoclonal FD0181G evaluated in a WHO workshop exciter, as a potential candidate for contraceptional studies, was used to screen the λgt11 lysate for suitable clones. The MoAb identified a clone expressing a 45 kD protein. This protein was isolated on PAGE and used to immunize rats. This would generate monospecific polyclonal sera needed for further studies. Other monoclonal antibodies such as T15 (courtesy Dr.B.L. Hai, Univ. of Nice, Paris) and PT 141.1 (courtesy Dr. U. W. Mueller, Australia), are also being employed to screen the library with the aim of identifying antigens that are potential candidates for antifertility vaccines.

Clinical trials with LHRH vaccine in prostate cancer patients

G.P.Talwar, Rahul Pal, Radhika Jayashankar, Subash Sad, Hema Malini Gupta and Dinakar Salunke with clinical collaboration of S.C. Sharma of the Postgraduate Institute of Medical Education and Research, Chandigarh, S.N.Wadhwa of the All India Institute of Medical Sciences, New Delhi and I. Frick, of the Urologiska Abteilung Landskronasanatoriet, Salzburg, Austria and V.Bracho and F.Alvares of Association Dominicana Pro Blanestar de la Familia, Santo Domingo.

A semisynthetic vaccine for LHRH that consistently induces bioeffective antibodies was reported the previous year. Extensive toxicology studies with the vaccine were conducted in both male and female animals, including sub-human primates. The vaccine blocked ovulation in females and impaired fertility in males. As expected, these effects were accompanied by a fall in sex steroid hormones. A marked effect of immunization was atrophy of the prostate gland in all male animals. With the approval of the Drug regulatory agencies and of Institutional Ethics Committees, clinical trials were started in terminal prostate cancer patients in two clinics in India and two overseas under the South-to-South cooperative programme in population sciences and reproductive health. The objective of the phase I/II trials is to determine the safety of immunization and absence of harmful side-effects. The vaccine is being employed at two dose-levels 200 or 400 µg. The immunization schedule consists of three injections spaced at six-week intervals for primary immunization, followed by a booster at 6 - 8 months and later as and when required.

Early results of these trials demonstrate the lack of side-effects of immunization in patients. The vaccine was effective in inducing antibodies reactive with LHRH. With the elevation of antibodies a fall in LH, FSH and testosterone was observed. This was however, preceded by momentary rise in gonadotropin levels. Clinical follow-up and data from ultrasonography indicates the beneficial effects of immunization in some patients.

Immunogenetic studies on the LHRH vaccine

Raj Raghupathy and Subash Sad

Immunization of male rats with LHRH conjugated to foreign carriers (such as diphtheria toxoid (DT) and tetanus toxoid (TT)) results in the generation of anti-LHRH antibodies and a subsequent decline in fertility in males and females. Interestingly enough, this immunization also brings about a marked atrophy of the prostate, thus offering possibilities of 'immunosurgery' in cases of hormone-dependent prostatic hyperplasia.

It is now well known that immunogenetic factors can influence an individuals immune responses to various antigens. In order to investigate the immunogenetic influences on responses to the LHRH vaccine (LHRH-DT), mice of different MHC haplotypes were immunized with the vaccine. Anti-LHRH antibody titres were estimated by a radioimmunoassay and anti-DT antibodies were estimated by ELISA. Substantial anti-LHRH antibody titres (ranging from 5 to 15 ng/ml antibody binding capacity) were found in mice of all strains immunized except one particular strain, 129, which was found to be a low responder to LHRH. Interestingly enough, the C57BL/6 strain which carries the same MHC haplotype (H-2^b) as 129, turned out to be high responders to the LHRH vaccine. By changing the carrier in the vaccine from DT to TT, it was possible to convert the initially hyporesponsive 129 strain to a high responder. The success of this 'alternate carrier approach' suggests that the hyporesponsiveness in the 129 mice is due to the carrier (DT). Experiments are now underway to ascertain whether 129 mice lack the ability to recognize helper epitopes that direct anti-LHRH responses or whether putative suppressor epitopes on DT down-regulate anti-LHRH

responses in a strain-specific manner. In order to better understand the role of the DT molecule as a carrier, helper and suppressor epitopes on DT are being delineated both by fragmenting the DT molecule and by analysing synthetic peptide segments from DT.

Another aspect of the immunogenetics of responses to LHRH-carrier conjugates is the effect that presensitization to the carrier has on antibody responses to the hapten (LHRH). Of the two strains of mice studied so far, a mouse of one strain (FVB/N) became hyporesponsive to LHRH after a single preimmunization with DT. This effect appears to be strain-specific since carrier presensitization does not have a discernible effect in the other strain studied (BALB/c). This finding could have implications in terms of post-vaccination responses and is being investigated further.

Structural studies on gonadotropin releasing hormone

Dinakar Salunke, Hema Malini Gupta, Navreena Grewal, Neetu Malhotra, Anil Pahuja, S.K.Gupta and G.P.Talwar

Three dimensional structure of gonadotropin releasing hormone (GnRH/LHRH) has hitherto not been elucidated. This information will enhance our understanding of molecular interaction of GnRH with antibodies and receptors of target tissues. Three complementary approaches are being followed in order to determine the structure of this molecule. These are, (a) Crystallography of different synthetic analogs of GnRH, (b) crystallography of GnRH-anti-GnRH Fab complex and (c) computer modelling of GnRH and its analogs employing a knowledge based approach.

Three GnRH analogs were synthesized and crystallization experiments were conducted. Some of these analogs show small crystals which can be clearly recognized by their birefringence properties. In a parallel approach crystals of Fab fragments of monoclonal antibody have been prepared which will serve as template for structural studies on GnRH. Appropriate size crystals of Fab fragments of anti-GnRH MoAb suitable for X-ray diffraction studies have already been obtained and experiments are in progress to diffuse the decapeptide in these crystals for co-crystallization.

The third approach involves computer modelling on the basis of sequence alignment, statistical analysis and energy minimization. A sequence data base corresponding to the proteins for which 3-D structures are deposited in the protein data bank has been used for an alignment search with five native GnRH sequences which have significant chemical analogy amongst themselves. A library of 90 structures which are analogous to these sequences have been made and the structures are being analyzed for conformational patterns.

Energy minimization and subsequent analysis of statistical distribution of the conformations of sequences selected from this library is currently in progress. Analogy search for 30 other small bioactive peptides was also carried out and preliminary analysis shows that the peptides in the size-range of 7 to 12 residues have substantially conserved three dimensional structures in different environments.

Immunization studies with sperm-specific antigen

Chandrima Shaha, T. Seshadri and Anil Suri

The previous report described the identification of 40 kD antigen on the human sperm and related 24 kD antigen on the rat testicular cytosol using antisera of rabbits immunized with whole human sperm. The 24 kD antigen purified from rat testes was used to immunize rats and monkeys. Antibodies could be detected in the serum and vaginal flushings of female rats orally immunized with this antigen. There was a significant reduction in fertility of rats as well as monkeys at high antibody titres. Immunized monkeys remained infertile for 5-6 cycles of observation. Sera from monkeys that had high antibody titres were analyzed for cross-reactivity at Dr. Shobha Sehgal's laboratory in PGIMER, Chandigarh. The antibodies did not cross-react with either smooth muscle tissue, nuclear proteins, parietal cells, mitochondrial proteins or islet cell proteins. The 24 kD antigen was analyzed by isoelectric focusing and was found to be composed of about 11 proteins of which only two were immunoreactive to the antisera. The two bands are being purified and their partial sequence determined.

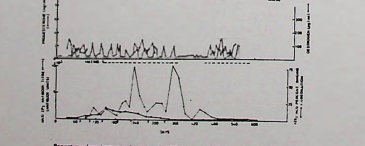
Sera having high titres of human sperm agglutinating antibodies derived from an infertile couple were used to delineate antigens from human sperm extract. An antigen approximating 80 kD on Western blot was identified. Interestingly enough, sera from both male and female partners reacted with this antigen. This antigen was found again to be conserved through evolution.

Immunofluorescence studies show that it is localized in the main tail piece of sperm of primates and on the acrosome of rodent sperm. Further characterization of this antigen is in progress.

Fertility regulation by 55 kD glycoprotein of the porcine oocyte

S.K.Gupta, Harini Bagavant and G.P.Talwar

The previous report described the results of active immunization of female bonnet monkeys with porcine zona pellucida-3 (ZP3), a highly purified 55 kD glycoprotein, either alone or conjugated to StxB. High titres of circulating anti-ZP3 antibodies were observed. Immunization did not, however, impair cyclicity or ovulation as monitored by progesterone and estradiol profiles and laparoscopic examination of the immunized animals. The animals were rendered infertile for over 18 months of observation period by repeated boosters. These animals are being followed up for the reversal of fertility subsequent to decline in anti-ZP3 antibody titres.



Bonnet monkeys immunized with purified ZP3, linked to BhCT. Boosters with ZP3 enhance anti-ZP3 antibodies without change in cyclicity or ovulation. Average for the days of maximum concentration (180 - 480). Animals do not conceive on mating with males of proven fertility

Monoclonal antibodies were generated against the ZP3 glycoprotein to delineate determinants on ZP3 that are involved in sperm-receptor recognition. Twelve MoAbs have been generated and are being characterized. All are specific to ZP in ELISA. All MoAbs, with the exception of MA-17 (against a subunit of ZP3) reacted with porcine oocyte in indirect immunofluorescent assay. This suggests that MA-17 recognizes a determinant on the α subunit which may be buried deeper within the zona pellucida. Some of the MoAbs specifically reacted to α or β-ZP3 and some were able to distinguish between their glycosylated and deglycosylated forms. These MoAbs will find utility in characterizing the role of ZP3 in the fertilization process and for definition of the smallest immunogenic capable of inducing infertility.

Antifertility effect of neem oil in female rats

Shakti N.Upadhyay, Charu Koushik, M.G. Sharma and G.P.Talwar

The oil of neem (*Azadirachta indica*) was investigated as an antifertility agent in rats. Female rats of proven fertility were administered 100 µl of neem oil by the intra-uterine route. The control rats were administered peanut oil. Animals from both the groups were put for continuous mating with males of proven fertility after administration of neem oil.

Animals immunized with neem oil remained infertile despite repeated matings for periods upto 180 days in contrast to control animals that became pregnant. Fertility in the former group could be regained and the litter size as well as the health of the delivered animals indicate that neem oil is not teratogenic.

Application of neem oil to only one uterine horn led to a fertilization block in that horn and the contralateral uterine horn was spared from this effect. There was no sign of implantation or fetal resorption in the uterine horn subjected to the treatment. The treatment did not alter responsiveness of the uterus to estradiol as evidenced by weight gain of the organ in ovariectomized animals. The uterine epithelium of all animals subjected to neem treatment exhibited leukocytic infiltration around day five post-coitum, the day corresponding to implantation of the embryo. The precise mechanism(s) responsible for inducing sterility whether it is a cellular immune response against the sperm or against the embryo is not defined yet. Investigations are in progress.

Meanwhile, experiments with neem oil have started on rabbits, bonnet monkeys and baboons. Preliminary results obtained from rabbits following a single intra-uterine administration of 200 µl of neem oil seem to confirm the results obtained with rats. Experiments on primates are in progress.

Intravaginal application of neem oil in bonnet monkeys induces transient infertility

M.G.Sharma. S.Joyammaan and G.P.Talwar

A number of therapeutic uses of neem are documented in literature. Neem oil has also been reported to be used as a vaginal contraceptive by different tribal populations. Sinha et al and Riar et al. have reported the spermicidal / anti-implantational and early abortifacient activities of neem oil and some of its active principles in rats, monkeys and women.

Investigations were undertaken in 14 (nine experimental and five control) colony acclimatized, fertile, regularly cycling female bonnet monkeys, to study the contraceptive potential of neem oil applied intravaginally. Six males of proven fertility were employed as partners to these females during the study. Experimental animals received 1 ml of neem oil administered intravaginally through a catheter, 10 minutes before they were set for mating.

The animals were allowed to mate daily for 5 menstrual cycles or till the females became pregnant, whichever was earlier. The cyclicity of the females, various hematological and blood biochemical parameters as indicators of systemic toxicity were carried out, before and during the study. Daily observations for the evidence of local adverse reaction in the reproductive passage were also made.

All the control females became pregnant within 2 cycles (5 conceptions in a total of 7 cycles) of initiating the study. One female in the experimental group became pregnant, while the others remained infertile during the study (1 conception in 40 cycles).

There were neither disturbances in cyclicity nor systemic or local adverse reactions during the study. The female from the experimental group that became pregnant following an accidental exposure to the male, delivered a normal, healthy infant at term. Three of the experimental females, on discontinuation of neem oil, became pregnant within 2 cycles. Observations suggest that neem oil has potential as a vaginal contraceptive.

Effect of intra-epididymal or intratesticular injections of neem oil in rat testes

Shakti Upadhyay, Charu Koushik and G.P.Talwar

Neem oil was investigated as a candidate contraceptive for male animals. Two groups of adult male WISTAR rats were injected with 50 µl of neem oil, intratesticularly or intra-epididymal on each side respectively. Animals were sacrificed two and four weeks after the injection. Testes and epididymides were excised and processed for high resolution light microscopy. It was observed that intratesticular administration did not arrest spermatogenesis. Infiltration of immune cells in the vicinity or oil droplets was observed. In contrast, histology of the testes of animals receiving intra-epididymal injections revealed that seminiferous tubules contained only early spermatogenic stages. There were no pathological indications in the testicular interstitium. Spermatogenesis was blocked two weeks post-injection. Circulating testosterone levels were comparable to that of normal unimmunized male rats. Epididymal ducts showed normal morphology and there was no evidence of inflammation. The changes brought about by immunization and possible reversal of infertile status, once immunizations are discontinued, are presently under investigation.

An intra-caudal injection with neem oil induces azoospermia in monkeys

Anil Suri, Sunil Chhabra and G.P.Talwar

It has already been established that a single intracaudal injection of BCG induces azoospermia in male monkeys (previous report). Neem oil was investigated as an agent for inducing azoospermia in monkeys. All monkeys demonstrated a fall in sperm counts within one month of administering the injection. Semen of monkeys subjected to the neem oil injection was sperm free. The circulating serum testosterone levels did not decline, showing normal functioning of Leydig cells. Further investigations are being carried out.

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Biennal Report 1988-1989
Geneva 1990

WHO-HRP- **Steering Committee of the Task Force on Vaccines for Fertility Regulation**

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Birth control vaccines

The central role played by vaccines in providing protection against many infectious diseases is now well accepted, and few people would disagree that vaccines have had a major positive impact on the health status of all the populations into which they have been introduced or that vaccination programmes form an essential part of any health care system. The use of vaccines to protect against unwanted pregnancy, however, is a comparatively new concept. Such vaccines would be particularly attractive for a number of reasons. For example: they would have a long-lasting protective effect after a single course of immunization; they would not cause menstrual-cycle disturbances and other hormone-dependent side-effects; they would be easy to administer by a well-accepted procedure; and they could be manufactured at low unit cost.

The three main criteria of drug development - safety, efficacy and acceptability - are particularly important in the development of anti-fertility vaccines, which are designed to work by generating immunity to one or more of the molecules involved in the reproductive process. To ensure that this immunity does not cause unacceptable metabolic disturbances and potentially hazardous side-effects, the Programme has decided to restrict its research activities to the development of vaccines based on molecules present only in, or on, or produced by, the sperm, the ovum (egg) and the pre-implantation embryo.

Anti-hCG vaccines

During 1988 and 1989 work has been concerned mainly with the further development and clinical testing of a vaccine directed against the hormone human chorionic gonadotrophin (hCG). This hormone, which is necessary for the establishment of pregnancy, is produced by the pre-implantation embryo perhaps as early as four days after fertilization. The purpose of the vaccine is to inhibit the function of hCG, thus preventing implantation of the embryo, which is expelled, together with the lining of the uterus, at the next menstruation, an event which occurs naturally.

During 1988, a Phase I clinical trial was completed on the safety of the prototype anti-hCG vaccine in previously sterilized women volunteers, and the results were analysed and published. The vaccine was apparently capable of producing immunity well in excess of that estimated to be needed to neutralize the biological activity of hCG, suggesting that this prototype may be capable of preventing pregnancy in fertile women.

A Phase II clinical trial is now planned to assess the vaccine's efficacy.

Before such a clinical trial can start, animal studies have to be done to determine whether any fetal abnormalities occur in the offspring of immunized animals, in order to assess the risks to the fetus should an unexpected pregnancy

WH 3.12

Jornal do Brasil 10.6.87

JORNAL DO BRASIL

9-6-87

Médica lembra que gravidez não é doença

Espanador ataca críticos de vacina anticoncepcional

LBA aceita o uso voluntário

Governo não atualiza dado demográfico

Ciência

Médica diz que gravidez não é doença a se tratar com vacina

WHO

RING

Progress

Although to date there have been no studies that compare the WHO vaginal ring with other hormonal contraceptives, data are available from several large-scale studies on various steroidal preparations that have been carried out by WHO over the past years. These data indicate that the WHO vaginal ring has a method failure rate comparable to the low-dose combination pill and the progesterone-releasing IUD.

The vaginal route of administration of contraceptive steroids offers a number of advantages over the oral or injectable steroidal preparations. First, the device can be inserted, removed and replaced by the user herself. Second, its position *in situ* can be checked easily, and corrected if necessary, by the user, which is not possible with IUDs. Third, since the ring has a constant release rate of the drug, a steady blood level of the steroid is maintained, which is not the case with oral contraceptives. Fourth, the total amount of steroid released by the ring over, for example, a period of one month is lower than any other hormonal method, being approximately 600 µg. Finally, the vaginal absorption of the steroid avoids the "first pass" effect of the liver, which means that the drug reaches the target organ without having first entered the enterohepatic circulation, thus reducing the risk of loss of the drug due to it being metabolized in the liver.

The Special Programme is also collaborating with the Population Council in the development and testing of a progesterone-releasing vaginal ring. It is expected that this ring will be particularly useful for post-partum contraception.

Phase I Clinical Trials start with an Antifertility Vaccine

After a decade of research and development, the first clinical trials of a WHO antifertility vaccine started in Adelaide, Australia, at the beginning of 1986. The active principle in this vaccine is a peptide immunogen that was specifically designed to elicit immunization against the hormone, human chorionic gonadotrophin (hCG). This hormone, which plays a crucial role in the establishment and maintenance of early pregnancy, is a particularly attractive target for an antifertility vaccine because during the non-pregnant state it is not produced in detectable amounts.

Although it is still early to say with certainty how successful this approach will be, preliminary data from the study have been quite promising. In the majority of women who have received this vaccine, including those in the lowest dose group, antibodies to hCG have been elicited, confirming the immunogenic properties of the synthetic peptide being tested. While, no unacceptable side-effects have so far been detected, some technical problems have been encountered with the formulation of the emulsion vehicle of the vaccine. Scientists are now trying to overcome these problems by developing alternative macromolecular carriers, adjuvants and delivery systems.

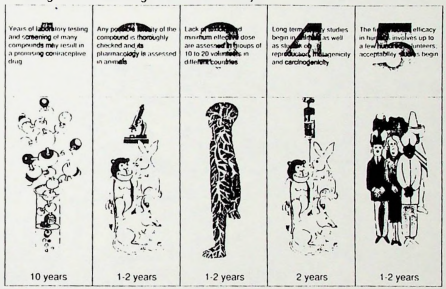
Potential advantages of an antifertility vaccine

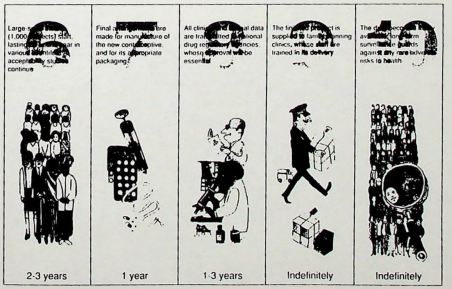
If and when safe and effective antifertility vaccines become available, they are expected to revolutionize family planning programmes. One obvious advantage will be that an antifertility effect of a fairly long duration (at least 1 year) will be achieved without the need for continuous administration of a pharmacologically active agent. Second, since they will be administered by injection, which is a well accepted and a simple procedure, it may be possible to distribute the vaccines using paramedical personnel. Third, although they will be long-acting, it is likely that their effect will be reversible. Finally, such vaccines are expected to lend themselves well to large scale synthesis and manufacture at a low cost. If all goes well the first antifertility vaccine should become available in the next five to ten years.

In addition to the WHO beta-hCG peptide vaccine, a number of other vaccines based on the whole beta subunit of the hormone human chorionic gonadotrophin are currently undergoing Phase I clinical trials. These preparations include a beta-hCG tetanus toxoid formulation developed by the Population Council, New York, USA, and several beta-hCG and alpha-ovine LH formulations, coupled to or mixed with tetanus toxoid and cholera chain B, developed by the National Institute of Immunology, New Delhi, India. The Special Programme is assisting with the coordination of research efforts in this area.

WHO - HRP 1990

Contraceptive Research
a long and winding road to safety..





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occur in a woman receiving the vaccine. The vaccine has been prepared and packed in accordance with Good Manufacturing Practice (GMP) requirements for materials intended for human use, and teratology studies - in rats, rabbits and baboons - are being conducted according to protocols approved by national drug regulatory authorities. In anticipation of a successful outcome, a protocol has been drawn up for the Phase II clinical trial and centres have been identified at which the trial might be conducted.

The prototype anti-hCG vaccine is a complex formulation unlikely to be suitable for large-scale production and use. The Programme has continued, therefore, with the development of better anti-hCG vaccines which could prove suitable for final product development. This work has included incorporating the immunogen and adjuvant components of the vaccine into microspheres formed from biodegradable/biocompatible polymers, which are capable of releasing the vaccine over a long period and have the potential to confer effective immunity lasting one year or more after a single injection. In addition, further work has been done on the design of new vaccine components of improved potency, specificity and clinical acceptability.

Anti-trophoblast vaccines

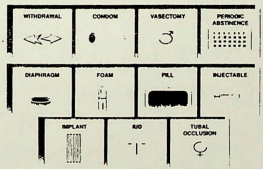
The Programme is also supporting studies to identify molecules that form part of the surface of the trophoblast of the pre-implantation embryo and might be suitable candidates for anti-trophoblast vaccines. Most previous studies in this area have used biochemical extraction procedures to isolate molecules that occur in relatively large amounts in the membrane of placental tissue. Molecules isolated in this way are then analysed to determine their amino-acid sequence, and from this information synthetic peptides can be made. The analytical procedures used are relatively harsh and unsuitable for isolating the molecules of most interest for vaccine development, namely those expressed for very short periods and/or in low concentrations during the pre-implantation stage of embryonic development.

To overcome this problem, the Programme has taken advantage of recent advances in the fields of immunology and molecular biology including monoclonal antibodies (MAbs). These MAbs can be used in a highly specific manner to detect and isolate molecules on the surface of trophoblast cells, which can then be assessed as candidates for vaccine development.

> Recombinant DNA technology is being used to determine the structure of these molecules so that they can be synthesized in the relatively large quantities needed for vaccine development.

Two proteins expressed on the surface of the trophoblast have been identified in this way and small amounts of these proteins have been prepared and tested for their ability to elicit a trophoblast-specific immune response capable of inhibiting fertility in female baboons. Some evidence of a partial reduction in fertility was obtained in this preliminary experiment and a further study in a larger number of baboons is now planned with the more potent of the materials. Additional MAbs are being generated and used to identify other trophoblast-specific molecules that might be suitable for vaccine development.

In order to manage the large amount of novel data being generated as a result of the Programme's studies in this area, a nomenclature system has been developed which will permit the establishment of a computerized data base containing information on trophoblast-specific MAbs and the molecules with which they react. A similar data base is also being developed for sperm-specific MAbs and the molecules with which they react on the sperm surface. These two nomenclature systems are being integrated into a joint data bank, the contents of which will be published at regular intervals and made available to investigators working in these areas.



'Freedom to choose means knowing all the choices.'

desired slow and prolonged release of vaccine, it was likely that a rapid and transient release had occurred, producing the reported myalgia and arthralgia and the poor anti-hCG antibody responses.

It was decided, therefore, to form two additional treatment groups, Groups IVa and Va, of eight more volunteers who would receive the same vaccine doses as the subjects in Groups IV and V but this time in an emulsion vehicle which had been made more stable by minor changes to the relative proportions of its constituents. This plan was approved by the appropriate drug regulatory committees and authorities, the subjects recruited and the immunizations carried out. The incidence and severity of the myalgia and arthralgia reported by the subjects in Groups IVa and Va were significantly less than those reported by their predecessors in Groups IV and V and were most evident in Group Va. These observations would suggest that the amount of MDP to be used, in this particular vaccine formulation, should be limited to the Group IV/IVa dose of 250 μg or less. The anti-hCG antibody responses in Groups IVa and Va were considerably improved and formed with the Groups I, II and III data, a clear dose-response pattern (Fig. 1), both in terms of antibody titres and, to a lesser extent, duration of antibody production.

Because of known species differences in the structures of baboon and human chorionic gonadotrophins and the time-course and mechanism of implantation in these two species, it is difficult to determine, from previous baboon antifertility studies, what levels of anti-hCG antibody will confer antifertility efficacy in the human. However, on the basis of the concentration of hCG in the maternal circulation at the time of implantation, it is estimated that an antibody level of approximately 0.5 nanomoles of hCG binding capacity would prevent implantation and thereby confer antifertility efficacy in women. As can be seen in Figure 1, this titre threshold has been exceeded in all of the five dose groups receiving the complete vaccine.

As part of the intensive analysis of the serum samples obtained in the course of this Phase I trial, immunofluorescent staining studies have been carried out to determine the incidence and nature of any tissue cross-reactivity exhibited by these sera (Burek et al, 1986a; Rose et al, 1988). A total of four serum samples were obtained from each of the 30 volunteers, in weeks 5, 7 and 26 after injection of the vaccine, with a pre-immunization sample serving as an individual-specific control in each case. These sera have been tested against a panel of rat, baboon and human tissues prepared as fresh cryostat sections (Burek et al, 1986b).

Virtually all sera exhibited reactivity against rat cardiac, skeletal and smooth muscle. However, the frequency and intensity of these reactions were essentially the same in the pre-immune sera as in the post-immunization samples and these results were not considered to be clinically significant.

Weak reactions against baboon pancreas were observed with samples from four individuals. These reactions were transient, appearing in samples taken five weeks after injection of the vaccine and disappearing by week 26. A closer examination of the stained sections indicated that the antisera were binding to somatostatin secreting cells in the pancreatic islets. However, this reactivity could not be absorbed out using purified somatostatin, in either the natural or straight-chain forms. Although no signs of pancreatic dysfunction and damage were seen in the preclinical baboon efficacy and safety studies, nor detected in the detailed histopathological examinations that were carried out on these animals postmortem, further studies are underway to identify the antigen involved and the long-term sequelae of this reaction.

Two of the 30 sets of sera exhibited binding with human pituitary sections. In the first case this activity was present only in the week 26 serum sample and not in any of the other samples from this individual; in the second case the reactivity was observed in all of the samples with the most intense reaction being exhibited by the pre-immune serum. A closer examination of the stained tissue indicated that binding was not specific to any one cell type and appeared to be randomly distributed and restricted to the

intracellular compartment. In view of the difficulties involved in obtaining fresh human tissues for definitive immunofluorescence studies, and the known artefacts that can occur as the result of non-specific reactions and postmortem changes in the tissue substrates, these results are not considered significant. However, studies are underway to characterize further the reactions observed, to identify the cell types and the antigen involved, and to determine the long-term sequelae of this apparent anibody binding.

With the successful completion of this first clinical trial of a synthetic peptide based antifertility vaccine, it is important to review the objectives of the trial, how well these objectives have been met, and the other information that has been obtained during the course of this study.

The results obtained in the Phase I clinical trial indicate that the Task Force's primary objective has been successfully achieved, in that the desired type of immunity has been elicited in most of the vaccine recipients without the production of unacceptable side effects. Furthermore, the antibody levels attained in all responders are estimated to be in excess of those expected to confer antifertility efficacy.

In view of these encouraging results, the Task Force is proposing to carry out a limited study with the current ß-hCG-CTP vaccine formulation, in a small number of fertile women volunteers, to determine if anti-hCG antibody levels in excess of 0.5 nanomoles of hCG binding capacity will provide an antifertility effect. However, before seeking approval to conduct this study in women it will be necessary to carry out further animal experiments in order to determine if any fetal abnormalities are associated with the vaccine's use. This will involve both an assessment of "chemical teratology" in rodents and rabbits as well as a concurrent assessment of "immunoteratology" in baboons or another relevant primate model. The latter study is particularly difficult to carry out in view of the paucity of background information in this area and the need to use a large number of animals in order to obtain statistically significant data. Although negative data will not be conclusive, the Task Force considers it important to attempt to obtain as much information as possible before conducting an efficacy evaluation of the current vaccine formulation in women. Protocols for these animal experiments and for the clinical study have been drafted in consultation with Task Force scientists and clinicians and with representatives of the pharmaceutical industry and national drug regulatory authorities. A further supply of the ß-hCG-CTP vaccine, needed for these additional animal and clinical studies, is currently being prepared, under the appropriate GMP conditions.

Valuable additional information has been obtained in the Phase I clinical trial, relevant to the development of a safe, effective and acceptable anti-hCG vaccine suitable for wide-scale application, particularly in the developing countries. This important information concerns all components of the current ß-hCG-peptide prototype vaccine formulation.

HCG Peptide: The 109-145 ß-hCG-peptide used in the current vaccine appears to be capable of eliciting anibody levels estimated to be several fold higher than that needed to confer antifertility efficacy. However, future vaccine production would be greatly facilitated if one or more short peptides of ß-hCG could be identified which retained the ability to elicit high levels of specific immunity to hCG and which were cheaper and easier to manufacture and characterize than the long peptide in the current formulation.

DT carrier: Out of a total of approximately 80 injections with the ß-hCG-CTP vaccine that were made during the course of the trial, adverse reactions to the DT components were seen in two instances. Whilst this may appear to be a very low incidence, it would probably be regarded as an unacceptably high level when large-scale use of the vaccine is considered.

Adjuvant: Comparison of the clinical trial data with those derived in the preclinical animal studies would suggest that the human dose of the MDP adjuvant need not exceed 200-250 μg in order to elicit adequate anti-hCG immunity. Limiting the MDP dose to this level would greatly reduce, and perhaps even eliminate, the

occassional and transient arthralgia and myalgia reported by some of the trial volunteers in the high-dose groups.

Vehicle: The complex and highly viscous emulsion used as the vehicle for the current vaccine is obviously not suitable for use beyond the preliminary stages of clinical testing. Although it may prove possible, by mechanical means, to produce a stable emulsion in a reliable and repeatable manner, the short duration of the immune response elicited by the ß-hCG-CTP vaccine delivered in this vehicle, necessitating frequent booster injections, would argue against its use in further vaccine development.

These findings justify the decision taken by the Task Force to evaluate a number of alternative formulations, as well as additional immunogens, immunostimulants and vaccine delivery systems, in order to produce improved vaccine preparations that will be suitable for eventual product development.

Development of improved and optimized anti-hCG vaccines

This work is being carried out in two phases. The first phase involves an evaluation of alternative delivery systems for the existing ß-hCG-CTP:DT immunogen and MDP adjuvant in order to find a replacement for the squalene-arlacel-water emulsion. In this area, the Task Force has continued with its studies on microsphere delivery systems, prepared with biocompatible and biodegradable polymers. The advantages of this particular approach to vaccine delivery are that microspheres can be individually engineered to meet the varied physico-chemical requirements of the different vaccine components, thus permitting the sustained release of the encapsulated vaccine over long periods of time and at predetermined release rates. It would be possible, therefore, to prepare vaccine formulations with pre-set durations of action ranging from a few months to several years. Furthermore, these preparations appear to be capable of eliciting high levels of anti-hCG immunity of long duration following a single injection of vaccine. Last but not least, this approach offers the added advantage of long-term vaccine stability under a wide range of climatic and storage conditions.

During the reporting period, a large number of microspheres, consisting of different ratios of polylactic and polyglycolic acid, have been prepared and evaluated in terms of their ability to elicit anti-hCG antibody titres of the required magnitude and duration. Four of these formulations produced titres which persisted, for at least six months, at levels in excess of those produced by the emulsion delivery system, and additional studies with the more promising of these formulations have indicated that anti-hCG antibodies can be elicited for a period in excess of twelve months. Additional supplies of the more promising preparations have been produced in larger quantities for further studies and a number of new formulations are also being prepared for comparative evaluations.

The second phase of this work is concerned with optimizing the anti-hCG vaccine to the point where it represents a safe, effective and acceptable pre-product formulation suitable for large-scale clinical trials. The studies being carried out in this area involve optimization of all components of the vaccine.

HCG peptide: The ß-hCG-CTP component of the immunogen in the current vaccine formulation, consists of a synthetic peptide 37 amino acids long. In spite of recent advances in chemical and biological peptide production methods, the preparation of a peptide of this length is still an expensive and difficult undertaking if the product is to meet the stringent specifications demanded by drug regulatory authorities. The Task Force has been conducting studies, therefore, to identify and subsequently evaluate a variety of additional peptides representing both sequential and conformational immunogenic determinants (epitopes) on the ß-hCG molecule (Stevens, 1986d).

The following summary of the studies carried out in this area over the reporting period, illustrates the complexity of this work and the potential offered by this approach for the development

of totally novel peptide immunogens, selected and engineered to provide enhanced immunogenicity whilst retaining specificity for hCG.

In natural ß-hCG, the amino acid residues forming the 38-57 region of the molecule exist as a loop structure formed by a disulfide linkage between the cysteine residues at each end of this peptide. Since previous studies with other molecules have demonstrated that such loop structures are potent immunogens, perhaps because of their prominent surface presentation on the molecule, a 38-57 loop peptide was synthesized and evaluated in rabbits. Although this loop peptide proved to be highly immunogenic, the antibodies raised to it cross-reacted with hLH. Further studies were carried out, therefore, with a number of intermediates of both straight chain and loop versions of the 38-57 peptide in order to develop an analogue capable of eliciting high levels of antibodies devoid of hLH cross-reactivity.

Comparative mapping studies have identified the 43-50 sequence as the hCG-specific epitope within the 38-57 peptide. An analogue of this epitope, consisting of the 43-50 straight chain peptide linked at its amino-terminal residue to a hexa-proline spacer, proved to be more immunogenic in generating hCG-specific antibodies than the 43-50 peptide alone but not as immunogenic as the 38-57 loop peptide.

Complementary studies were carried out to define the regions within the 38-57 loop peptide that were responsible for eliciting antibodies crossreacting with hLH. These activities were found to reside in the regions, 30-42, 45-57 and 50-62 of the molecule. On the basis of the information gained from these studies, three experimental loop peptides have been prepared with amino acid substiutions designed to remove the hLH crossreactivity and to confer some degree of α helical structure on the peptide. One of these "helical" peptides has been found to be more immunogenic than its straight chain counterpart, and whilst it is not as immunogenic as the native 38-57 loop, it does produce antibodies specific for hCG. When this peptide is given, as a combined immunogen with the 109-145 ß-hCG-CTP, antibodies are elicited at levels much higher than those produced by either of the peptides alone. In addition, other surface epitopes on the beta-hCG molecule have been identified using predictive rules for molecular structure or by the binding properties of ß-hCG specific monoclonal antibodies. Peptides representing some of these epitopes have been synthesized and evaluated and a number of regions on the ß-hCG molecule have been identified which could form the basis for the development of new anti-hCG immunogens. These data indicate that immunogens consisting of a number of short and novel peptides, selected on the basis of their immunogenicity and hCG specificity, could form the basis of a prototype second generation anti-hCG vaccine meeting the Task Force's requirements.

New carriers: The carrier molecule used in the first generation anti-hCG vaccine is a purified form of clinical grade diphtheria toxoid (DT). Although this DT is a single molecular weight fraction, it is still a chemically ill-defined and heterogeneous preparation. Furthermore, the repeated use of a vaccine incorporating this material produces a low but significant incidence of delayed type hypersensitivity (DTH) reactions. As stated earlier, such DTH reactions were observed in two out of 30 women receiving the complete vaccine formulation in the Phase I trial. Although this incidence of DTH reactions presents no difficulties in the context of a small-scale clinical trial, it is almost certainly too high to permit a DT-containing vaccine to be considered for wide-scale clinical use.

The Task Force has continued, therefore, with its search for clinically acceptable molecules to evaluate as alternative carriers for the hCG peptide immunogens. In studies carried out with ß-hCG peptides conjugated to a purified protein derivative (PPD), obtained originally from *Mycobacterium tuberculosis*, good anti-hCG antibody responses were elicited and the frequency and intensity of DTH reactions were found to be much lower than those produced by conjugates containing DT. Further studies are planned with single molecular weight species of *M. leprae* PPD obtained by recombinant DNA procedures.

The principal advantage of these materials is that their chemical structures are known. However, they do have a major disadvantage in that they will not confer protection against tuberculosis but will render recipients skin test positive on subsequent challenge. The clinical and epidemiological implications of this "false positivity" would need to be carefully discussed before embarking on a major research programme to develop an anti-hCG vaccine, or any other vaccine, incorporating these materials as the carrier component of the immunogen.

New adjuvants: Although the MDP analogue in the current vaccine formulation has been approved for use in clinical trials, it may not be suitable for inclusion in a vaccine for wide-scale clinical use except at lower doses which may not confer immunity of sufficient magnitude or length in all recipients. There are a large number of additional MDP analogues and other experimental immunostimulants available, but the amount of immunological, pharmacological and toxicological informaiion on these compounds is limited and is not sufficient to permit the selection of an alternative preparation suitable for clinical trials. The Task Force is continuing, therefore, with its studies to compare the properties of alternative immunostimulants that might be suitable for clinical use.

A number of thiol compounds have been tested during the reporting period in an effort to identify a clinically acceptable alternative to MDP, but none was found to be suitable for this purpose. Although no further studies are planned with these particular compounds, these studies did allow the confirmation of earlier findings that an adjuvant may be needed only in the first injection for a vaccine to elicit an adequate immune response.

New delivery systems: As indicated earlier in this chapter, the vehicle used in the prototype hCG vaccine is a high-viscosity water-in-oil emulsion which requires careful preparation immediately prior to injection. Although it is possible that the *in vitro* and *in vivo* instability problems encountered in the Phase I clinical trial might be overcome by preparing the emulsion using a machine capable of achieving high shear forces, it is unlikely that a vaccine for widespread clinical application will be administered in this form in view of the limited duration of the immune response elicited by preparations administered in this vehicle. The Task Force has continued, therefore, with its studies to develop and evaluate alternative delivery systems capable of producing an effective level of anti-hCG immunity of long duration, preferably following a single injection of vaccine. In addition to the work with copolymer microspheres referred to earlier, the Task Force has also carried out experiments in rabbits with a number of liposome and iscom (immunostimulating complexes) preparations, incorporating various combinations of the ß-hCG-CTP:DT conjugate and MDP adjuvant.

Both of these vaccine delivery systems appear to be well tolerated by the experimental animals and elicit substantial levels of anti-hCG immunity. However, in terms of duration of effect, neither liposomes nor iscoms proved to be as effective as the microspheres.

Development of a baboon CG vaccine

Although the primate chorionic gonadotrophins appear to have the same physiological functions, there are substantial species differences in the chemical structures of these hormones and in their secretion profiles throughout gestation. As a result of these species differences, antibodies raised in baboons to the heterologous ß-hCG-CTP vaccine cross-react with endogenous baboon CG (bCG) by approximately 5% compared to hCG. Whilst this comparatively low level of crossreaction is sufficient to produce an antifertility effect in the immunized baboons, it may not be sufficient to stimulate, either qualitatively or quantitatively, all of the acute or chronic side-effects that might occur when the homologous ß-hCG-CTP vaccine preparation is used in women.

The Task Force has continued, therefore, with its programme to develop a baboon model system in which a vaccine based on the animal's own CG can be used to evaluate extensively these safety issues. These studies have proved

technically difficult and costly and have not yet been satisfactorily completed. If solutions can be found to the technical problems encountered, it may prove possible to develop a ß-bCG-CTP vaccine that is equivalent to the ß-hCG-CTP preparation. This anti-bCG vaccine would enable more meaningful data to be generated in baboons concerning the safety of this novel approach to fertility regulation.

The first step in the development of a ß-bCG-CTP vaccine is the elucidation of the amino acid sequence of the baboon hormone in order that the appropriate peptide can be synthesized. These studies have followed two separate but complementary approaches.

In the first set of studies, bCG is isolated from baboon pregnancy urine and purified for subsequent classical protein sequence analysis. Major unforeseen problems and delays have been encountered in this programme, resulting from the transient nature of the secretion of the baboon hormone, its inherent lability, and the difficulties of collecting sufficient quantities of baboon pregnancy urine in an uncontaminated form. Improvements have been made continuously by Task Force scientists in the procedures used for the collection of baboon pregnancy urine and its subsequent processing to obtain urinary bCG. Recently, several milligrams of purified bCG have been prepared with a biological activity corresponding to 10,000 IU of hCG per mg from which the ß subunit has been isolated for amino acid sequence analysis. In accordance with established protein sequencing procedures, the ß-bCG has been subjected to enzymatic digestion in order to obtain fragments of the molecule that can be analyzed using automated equipment. These fragments have been purified and separated by reverse-phase HPLC to yield 6-8 fractions with different physicochemical properties reflecting their location in the ß-bCG molecule. Preliminary amino acid analyses on these fractions are currently underway and it is anticipated that a tentative structure for part or all of this molecule might be available early in 1988.

In the second set of studies, recombinant DNA techniques have been used to determine the nucleotide sequence of the bCG gene, from which the amino acid sequence of the hormone can be deduced. These studies have identified several genes coding for CG in the baboon placenta, and it is not clear how many of these genes there are, how closely related they are to each other, or which one is responsible for producing the physiologically and immunologically important form of bCG. In an attempt to resolve these issues, the Task Force has carried out studies to assess the biospecency and immunological reactivity of heterodimers, consisting of the α subunit of bovine LH and the alleged ß subunit of bCG, produced using a mammalian cell expression system. The gonadotrophic potencies of the expressed products have been determined using the Leydig cell bioassay, and their immunological reactivities have been assessed in radioimmunoassay (RIA) using monoclonal and polyclonal antisera to ß-hCG-CTP and the proposed baboon counterpart. To verify the authenticity of the expressed materials, autoradiographic studies have been carried out to determine their presence and location in human and baboon placentae.

None of the expressed heterodimer products obtained so far has exhibited the appropriate activities in all of these systems. From the available data, it is not clear if the expressed material is a gonadotrophin or another, irrelevant, gene product. Comparative studies are underway to determine if one of the other bCG genes in the baboon placenta codes for a more relevant material than that already studied, and further RIA studies are also underway to determine the tissue specificity and localization of the putative antigenic material.

It is anticipated that a definitive answer to the bCG sequence question will be provided from the purified baboon pregnancy urine material (Bambra, 1987), either directly by total amino acid sequence analysis, or indirectly by using partial amino acid sequence data to prepare oligonucleotide probes for screening gene libraries prepared from baboon placentae at the peak of bCG secretion. The relative molecular sizes of the naturally occurring and expressed materials will be compared using electrophoresis, immunoblot procedures and autoradiography.

From the data generated in these two complementary research activities, it should prove possible to detect and characterize the C-terminal region of ß-bCG and to synthesize the appropriate peptide for formulation into a ß-bCG-CTP vaccine.

Once a relevant ß-bCG-CTP vaccine has been prepared, meaningful studies can be carried out in the baboon to assess the efficacy and safety of this homologous preparation. A successful outcome to these studies will provide greater confidence for proceeding to a clinical evaluation of the antifertility efficacy of the the current ß-hCG-CTP vaccine as well as for the development of improved anti-hCG vaccine formulations suitable for wide-scale clinical application.

Development of an anti-trophoblast vaccine

At its meeting in September 1985, the Special Programme's Scientific and Technical Advisory Group (STAG) recommended that the Task Force should expand its activities to include studies on additional targets for FRV development. In order not to duplicate the work of other agencies in this area, which is largely restricted to the development of anti-gamete vaccines, the Task Force has initiated studies on a vaccine based on membrane antigens of the early trophoblast. Although there are many investigators working on the immunobiology of the early trophoblast, this is largely in terms of its role in preventing immunological rejection of the "fetal allograft", and the Task Force studies are the only international, multidisciplinary collaborative vaccine development programme in this area.

Previous studies carried out, both by Task Force scientists and other investigators, had focused on the identification of membrane expressed molecules that could be isolated from the trophoblast using classical mechanical and biochemical extraction procedures (Johnson, 1985; Stern et al, 1987). The comparative harshness of this approach can result in the partial or complete destruction of the more labile membrane components, many of which may be molecules of interest for vaccine development. The Task Force has decided, therefore, to use a combination of monoclonal antibodies (MABs) and molecular genetics techniques to identify, isolate and characterize trophoblast membrane antigens that might represent suitable candidates for development into anti-trophoblast vaccines.

The research strategy being employed by the Task Force in this area involves the use of MABs that satisfy the following three criteria:

-- tissue-specificity for human trophoblast;

-- cross-reactivity with similar or equivalent tissues in other mammalian species;

-- ability to disrupt or inhibit the function of trophoblast *in vitro* and/or *in vivo*.

By establishing these three criteria at the outset of its studies, the Task Force is aiming to develop anti-trophoblast vaccines which will not produce cross-reactions to other non-target tissues; which can be evaluated for safety and efficacy in a relevant animal model; and which will be directed against antigens expressed on the cell surface, and which are accessible, therefore, to antibodies and immune cells in the maternal circulation. MABs satisfying these three criteria can then be used to isolate antigens expressed on the surface of the trophoblast membrane and to screen the products of expression systems in which genes coding for trophoblast antigens have been inserted. The data generated in these studies will permit a range of synthetic peptide immunogens to be prepared for comparative evaluations of their potencies as anti-trophoblast vaccine components.

As an initial step in this new research programme, the Task Force has carried out a systematic evaluation of a large number of anti-trophoblast monoclonal antibodies that had already been produced by investigators in the field. The data generated in these studies were reviewed and discussed at a workshop (Anderson et al, 1987), jointly organized by WHO and Family Health International (FHI), and held in Toronto, Canada, in June 1986 in conjunction with the third International

Congress on Reproductive Immunology and the sixth International Congress of Immunology. A total of 44 such antibodies alleged to satisfy the primary criterion of trophoblast specificity were obtained from 15 investigators and further characterized, in coded form, in terms of the types of tissue with which they reacted, the location of these reactions within the tissue, and the nature of the putative antigenic material. The results obtained in these preliminary studies are summarized in Table 2.

Species cross-reactivity was assessed against baboon, marmoset, donkey, horse, cow, pig and rodent placentae. Five of the 44 MABs exhibited tissue-specific cross-reactivity with baboon placental tissue and many exhibited a variable degree of cross-reactivity with rodent placental or embryonic tissues. However, the data generated with rodent tissues showed poor correlation between investigating laboratories.

Tissue location and antigen characterization studies were carried out on detergent-solubilized isolated human placental syncytiotrophoblast plasma membranes using immunoblot and radioimmunoprecipitation techniques. In the immunoblot studies, five of the 44 MABs reacted with clearly defined bands of solubilized material with molecular weights of approximately 115 kDa, and 14 MABs identified protein antigens in the radioimmunoprecipitation studies. Further immunohistological studies and enzyme capture assays indicated that four out of the five MABS that reacted with solubilized material in the immunoblot experiments were directed against heat-stable placental-like alkaline phosphatase (PLAP) and an additional four MABs appeared to be directed against the cell surface receptor for transferrin. However, five other MABs appeared to react to novel solubilized components of placental syncytiotrophoblast plasma membrane and two of these MABs also reacted with baboon placental tissue. These two MABs appeared to be directed against two glycoprotein antigens with molecular weights of 43 kDa and 76 kDa, respectively.

These preliminary studies have identified, therefore, at least two and perhaps as many as five MABs, out of the original group of 44, that

Table 2. Tissue reactivities of anti-trophoblast monoclonal antibodies

Tissue reactivity observed	Number of monoclonal antibodies
First trimester and term human placenta	19
Term human placenta only	6
Extensive cross-reactivities with other human tissues	11
Non-reactive with first trimester and term human placenta	8

appear to satisfy two of the three criteria established by the Task Force. Further studies are underway and planned with these high priority reagents in order to isolate and characterize the trophoblast membrane protein antigens with which they react as a prelude to the synthesis of these materials for evaluation in prototype anti-trophoblast vaccines. The Task Force is maintaining contacts with investigators working in this field and further MABs, meeting the same stringent requirements, will be added to this panel of reagents as they become available.

Progress has been made also in the recombinant DNA project which is being carried out to complement the MAB studies. A human placental gene library has been established and vectors containing cDNA coding for human placental proteins have been inserted into cloned mammalian host cells. The high priority MABs will be used to screen these host cells for the presence of relevant human placental gene products expressed on their plasma membranes. Clones exhibiting the desired expression products will be expanded to obtain sufficient quantities of genetic material, or expressed protein, for the sequence analyses needed prior to the synthesis of peptides for subsequent evaluation as candidate immunogens for anti-trophoblast vaccines.

Table 3. Tissue reactivities of anti-sperm monoclonal antibodies (MABs)

Tissue and other reactivities observed	Number of MABs tested	Number of MABs reacting
Live human sperm surface, before/after washing, and before/after capacitation	66	32
Human testis, seminiferous tubules only	66	9
Human testis, interstitial compartment only/also	66	24
LDH-C4 neutralizing activity	49	11
Cross-reactivities with other human tissues	60	33

Development of an anti-sperm vaccine

Studies on anti-gamete vaccines, which are likely to be effective prior to fertilization, have been supported by the Task Force in the past (Hjort and Griffin, 1985; Hjort et al, 1985; Mori et al, 1985; Shelton and Goldberg, 1985; Wang et al, 1986) and are being supported currently by several national and international funding agencies (Bronson et al, 1985; Czuppon, 1985; Lehmann et al, 1985; Mathur et al, 1985; Mettler et al, 1985). In order to avoid duplication of effort, the Task Force is not funding a major research programme in this area. However, it is conducting a systematic evaluation of anti-sperm MABs in order to characterize these reagents in terms of their abilities to:

-- react specifically with human late spermatids and mature spermatozoa;

-- cross-react with similar or equivalent cellular stages of spermatogenesis in other mammalian species;

-- interfere with sperm motility or inhibit sperm-ovum attachment and fertilization *in vitro* and/or *in vivo*.

The overall objectives of these studies are similar to those described for anti-trophoblast MABs in the preceding section of this report, namely to identify MABs that can be used to isolate and characterize sperm membrane antigens that represent appropriate candidates for development into anti-sperm vaccines.

Again, as the initial step in this new research programme, the Task Force has carried out a systematic evaluation of a large number of anti-sperm MABs that had already been produced by investigators in the field. The data generated in these studies were reviewed and discussed at the workshop (Anderson et al, 1987), jointly organized by WHO and Family Health International (FHI), and held in Toronto, Canada, in June 1986 in conjunction with the third International Congress on Reproductive Immunology and the sixth International Congress of Immunology. A total of 66 such antibodies, alleged to satisfy the primary criterion of sperm specificity, were obtained from 17 investigators and further characterized, in coded form, in terms of the types of tissue with which they reacted, the location of these reactions within the tissue, and the nature of the putative antigenic material.

Tissue location studies were carried out, by immunofluorescence and immunoperoxidase staining procedures, on human testis sections (to distinguish between reactions with components of the seminiferous tubules and the interstitial compartment of this organ), and on a large number of other normal human tissues and fluids. Some of the MABs were assessed for their abilities to neutralize the enzymic action of the sperm-specific lactate dehydrogenase isozyme, LDH-C4. The results obtained in these preliminary studies are summarized in Table 3.

Species cross-reactivity was assessed against a variety of primates (gorilla, orangutan, rhesus monkey, baboon, chimpanzee, marmoset) and other species (elephant, hamster, rat, mouse, horse, mountain sheep, dog). Eighteen MABs cross-reacted with sperm from at least one non-human primate species and 21 cross-reacted with mouse sperm in at least one laboratory. Wide species cross-reactivities were exhibited by four MABs.

A variety of tests were carried out to assess the inhibitory activity of the MABs on sperm function. These included inhibition of sperm motility, sperm agglutination, sperm immobilization, inhibition of cervical mucus penetration, and inhibition of the penetration of hamster ova by human sperm. The results obtained in these functional tests are summarized in Table 4.

Four laboratories have carried out studies in an attempt to derive information on the physicochemical properties of the human sperm antigens identified by selected sperm-specific MABs. Although the results obtained by these laboratories did not correlate well, the more relevant materials identified in this way have molecular weights in the range 15-30 kDa.

These preliminary studies have identified six MABs, out of the original group of 66, that appear to satisfy the criteria established by the Task Force. In addition, these studies have demonstrated a considerable variability in surface expression of most sperm antigens identified by sperm-specific MABs. This variability may be a product of the wide variation of immunizing materials used by different investigators as well as a reflection of the inherent polymorphism of these antigens. In addition, antigenic expression on the sperm surface can be affected by the known and suspected changes that occur as a result of passive coating with seminal plasma

Table 4. Activities of anti-sperm monoclonal antibodies in sperm function tests

Functional test	Number of MABs tested	Number of MABs active
Inhibition of sperm motility	62	22
Sperm agglutination	55	15
Sperm immobilization	55	8
Inhibition of cervical mucus penetration	35	8
Inhibition of hamster ovum penetration	53	25

components, enzymatic modification as well as the stage-specific structural changes associated with maturation, capacitation and the acrosome reaction.

In view of the confusing and often conflicting data being generated in this area, the Task Force has initiated a sperm antigen classification project. This project is modelled on other WHO-sponsored nomenclature programmes in other fields (for example leucocyte and parasite antigens) and will establish an organized data base and nomenclature system specifically for human sperm antigens. Initially, the work to be carried out will form an extension of the studies already conducted by the Task Force and will involve the collection, banking, distribution and characterization of anti-sperm MABs with a final objective of producing a computerized data base in which each sperm-specific antigen will be identified by a project-assigned WHO code number.

FUTURE DIRECTIONS

The Task Force is proposing to carry out the following activities during the 1988/89 biennium.

Subject to a satisfactory outcome of animal teratology studies, approval will be sought to carry out a limited efficacy evaluation of the current anti-hCG vaccine formulation in fertile women volunteers. In addition, the Task Force will continue with the development of an improved version of this vaccine, using a slow-release delivery system designed to elicit long-lasting immunity from a single course of immunization, as well as the development of a second generation of anti-hCG vaccine that will represent a viable product prototype. This latter work will involve the systematic development and comparative evaluation of additional synthetic peptide immunogens, carrier molecules, adjuvants and delivery systems in order to produce a vaccine that is clinically acceptable, appropriate for product development, and suitable for wide-scale application in family planning programmes.

Antifertility studies will be carried out in animals to evaluate prototype anti-trophoblast vaccines. The antigens to be used in these vaccines will have been identified by characterization of trophoblast membrane extracts and by screening gene libraries from human placentae, using selected anti-trophoblast MABs that satisfy the Task Force's criteria of tissue-specificity, lack of species-specificity, and a function-inhibiting or disrupting action.

The Task Force will continue with its recently initiated programme to classify sperm-specific MABs, with a view to characterizing sperm membrane antigens that might represent suitable candidates for development into anti-sperm vaccines. It is envisaged that this work will be conducted in close collaboration with the Task Force on Methods for the Regulation of Male Fertility and with other agencies active in this area. In addition, developments in the field of zona pellucida immunobiology, local (secretory) immunity and 'basic vaccinology' will be monitored in terms of their relevance to the development of antifertility vaccines.

The Task Force is planning to convene a meeting on vaccine safety in order to develop guidelines for the preclinical and clinical safety evaluations of vaccines in general and for antifertility vaccines in particular. It is envisaged that this meeting will be organized in conjunction with other vaccine development programmes within WHO and with other agencies interested in the development of antifertility vaccines. Basic and clinical scientists, representatives of national drug regulatory authorities, the pharmaceutical industry and consumer groups will be invited to participate in this meeting.

The Task Force will continue with its coordination activities in the field of fertility regulating vaccines. As in the past, this coordination will include participation in Task Force Steering Committee meetings by representatives of CONRAD, the Population Council, the Indian National Institute of Immunology and the US National Institute of Child Health and Human Development; the convening of inter-agency consultations; organization of symposia; and the joint funding of research projects of mutual interest.

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Biotechnology in India

Nagesh Kumar

The recent advances in biotechnology provide to developing countries valuable means to step up their development process and eradicate more effectively the poverty, hunger, and disease even though in the immediate future they would affect their commodity exports.[1] The Indian government recognised the potential of biotechnology and in the last few years took a series of initiatives to promote biotechnology research in the country. This note outlines the potential of biotechnology in India and the factors that favour the entry of the country in the field and reviews the evolution of the Indian government policy and programmes to strengthen biotechnology research in the country. It also examines the current status of biotechnology industry in India and concludes with some remarks for the future policy.

The potential

The new plant breeding techniques involving genetic engineering, protoplast fusion, and tissue culture make development of high yielding varieties far easier and rapid. Therefore, it has been argued that biotechnology can help in manifold expansion of agricultural output in India. Besides high productivity, the varieties developed through new breeding techniques can be made resistant to disease, pests and herbicides. It is possible also to incorporate features of different plants such as nitrogen fixation in case of legumes and succulent metabolism of cactus into the new varieties.[2] The biorevolution, as against Green Revolution, therefore, can help in saving of resources spent on pesticides, fertiliser, irrigation etc. leading to low costs of product. Biotechnology can also help address the perennial shortages of edible oils and pulses in the country. Tissue culture techniques can help in propagation of high yielding, disease resistant and fast growing varieties of coconut and oil palms to quickly increase the edible oil production. The same technique can also help in improving the quality and yield of fruits and other vegetatively propagated plants. Edible fats can be produced from rice straw. Just 40% of rice straw available in the country can produce fat equivalent to annual edible oil consumption.[3] Hence, biotechnology can help the country obtain self-sufficiency in edible oils and save foreign exchange worth about Rs. 10 billion a year.

Besides biological nitrogen fixation, the biofertilizers such as blue-green algae contributes 25 to 30 kilogrammes of nitrogen per hectare per cropping season.[4] They can, therefore, help the country save on fertiliser imports (current imports valued at about Rs. 13 billion per year).

New microbial techniques can convert biomass into energy and therefore, offer to the country a potentially rich renewable source of energy. Besides contributing to saving of foreign exchange, biomass — energy systems may help in creation of employment and income in India's rural areas and make them self-sufficient in their energy needs. Biotechnological breeding techniques such as embryo transfer can help in achieving fast growth of dairying and poultry farming. The milk production can also be boosted with the help of growth hormones produced through biotechnology. In the sphere of health, bio-diagnostic kits can help in early detection of diseases. A number of hormones and vaccines can be produced with the help of biotechnology outside animal bodies. In mining, bacterial leaching can be used for extraction of low grade minerals. In a number of food processing industries using bio-chemical reaction, productivity can be increased with the help of new strains of microorganisms and energy saving can be effected.

India's advantages in biotechnology

Among the developing countries India is perhaps one of the most uniquely placed to tap the potential of biotechnology for its development. One of the factors which facilitate the entry of the country in biotechnology research is its well developed scientific and technological infrastructure. A large number of national laboratories in the framework of Indian Council of Agricultural Research, Council of Scientific and Industrial Research, and Indian Council of Medical Research have already been engaged in basic and applied aspects of genetic, microbial and cellular biology research. It is, therefore, a question of largely upgrading the existing capabilities. Similarly, a vast pool of technical manpower and scientists is available who could be oriented into biotechnological techniques with some training. As one of the tropical countries, India is endowed with rich genetic heritage both in animals and plants. India has a well developed and diversified industrial base including a strong public sector committed to national priorities. The industry in India has, in recent years, shown a growing inclination towards scientific entrepreneurship, as reflected in growth in number of in-house R & D units. This can help in quick commercialisation of advances in laboratories. Furthermore, the biological research costs in India are relatively lower than in Western countries. For instance, work in microorganisms require animal houses. Tests involving small animals in India cost only a twentieth or twenty fifth of that in Europe or in United States. In the case of primates, Indian costs are one-fifth.[5] Finally, the large size of the country allows it to undertake ambitious research programmes on viable basis. Besides, biotechnologies by nature are relatively open, versatile and less capital intensive and there can be many routes of developing a product. These features in general imply that the entry barriers to biotechnology are relatively lower than other new and high technologies such as microelectronics.

Government policy and planning

The Sixth Five Year Plan of India's development (1980-85) was the first policy document to cover biotechnology development in the country. In the sphere of Science and Technology (S & T) sector, the Plan had indicated that "the effort would be to strengthen and develop capabilities in new areas such as immunology, genetics including molecular biology and genetic engineering for control of intractable communicable diseases viz. Malaria, leprosy, filariasis and kalaazar." Furthermore in respect of the Council of Scientific and Industrial Research (CSIR) the Plan notes "Attention in the Sixth Plan period would be directed towards project-oriented and mission oriented research with close coordination on an inter-institutional, inter-agency and multi-disciplinary basis, with full utilization of existing facilities and infrastructure" as major areas indicating biotechnology. Programmes in the area of biotechnologies included; tissue culture application for medicinal and economic plants; fermentation technology and enzyme engineering for chemicals, antibiotics and other medical products development; agricultural and forest residues and slaughter house wastes utilisation, emerging areas like genetic engineering and molecular biology.[6] Though the existing national laboratories under the S & T agencies such as Indian Council of Medical Research (ICMR) and CSIR had initiated research programmes to fulfill the above Plan objectives, an apex official agency viz. National Biotechnology Board (NBTB) was set up in 1982 to spearhead development of biotechnology. The NBTB was chaired by Member (Science) of the Indian Planning Commission and had representation of almost all the S & T agencies in the country viz. Department of Science and Technology, CSIR, Indian Council of Agricultural Research (ICAR), ICMR, Department of Atomic Energy (DAE) and the University Grants Commission (UGC). NBTB was formed with the specific purpose of the identification of priority areas and for evolving a long term plan for the country in biotechnology as well as to initiate and promote such activities as conducive for further development of various areas in biotechnology. The NBTB issued in April 1983, the *Long Term Plan in Biotechnology for India*. This document spells out priorities for biotechnology in India in view of the national objectives such as self sufficiency in food, clothing, and housing, adequate health and hygiene, provision of adequate energy and transportation, protection of environment, gainful employment, industrial growth and balance in international trade. These priorities in seven broad areas viz. health, industry, agriculture, energy, environment, communication and informatics, and education and training are given in Table I. The Plan also formulates specific projects to fulfil the priorities with time horizons ranging from 3 to 10 years (Table II). The emphasis in the area of health is on production of vaccines, hormones and antibodies for a variety of tropical diseases and population control. In agriculture, it is biological nitrogen fixation and biofertilizers, biological control of insects, development of disease resistant and stress tolerant varieties of crops using tissue culture, somatic hybridisation and selection technology, improving nutrition and quality of food grains and rapid propagation of high yielding vegetables and fruits.[7].

Besides formulating the long term plan, the NBTB evolved programmes in integrated manpower development in biotechnology, funding of R & D projects and programmes, drew up plans for creation of infrastructural facilities and production of vaccines. It evolved mechanisms for supply of radio-labelled chemicals and production and import of restricted enzymes for genetic engineering research.[8] The programmes and schemes are being implemented in the Seventh Five Year Plan (1985-90).

The Seventh Plan in the area of biotechnology gives emphasis on programmes connected with manpower development; institution of new projects and programmes involving multi-disciplinary and multi-institutional participation, together with necessary linkages with industry, involving techno-economic feasibility studies; providing seed and risk capital in establishing large-scale applications using technologies developed within the country; and setting up manufacture based assessment (R & D) of products based on modern biotechnology. The necessary infrastructure like germ plasma banks, pilot plant and other bio-engineering scale-up facilities, network of biotechnology information systems, animal house facilities etc. would also be set up. In addition, production and manufacturing units for vaccine against major diseases, and production of plasma, serum, hormones and enzymes would be taken up. It is expected that by 1990 some of the major vaccine needed for the Expanded Programmes of Immunisation would be produced indigenously on a large-scale, using modern techniques.[9] Besides the CSIR proposed to complete the establishment of the Institute of Microbial Technology, Chandigarh; Centre for Cellular and Molecular Biology, Hyderabad and proposed to take up basic research in cellular and molecular biology.[10] In the area of medical research the Plan document recognised that "the cutting edge of biomedical re-

Table I - Priorities for Biotechnology in India

Priorities	
Health	Energy
Prophylactic	Biomass
Therapeutic	Energy Plantation
Diagnostic	Biofuels and Bioreactors
Hygiene	
Population Control	Environment
Industry	Conservation of Forests and Afforestation
Fermentation (Antibiotics, Organic Acids)	Pollution Recycling
Biofuels	Waste Recycling
Food and Feed	Communication, Informatics
Metallurgy and Mining	Computer Based Information
Oil Recovery	Collection and Dissemination
Agriculture	Education and Training
Soil Fertility	University Level Education
Bio-Fertilizers	Specialized Training Program
New Varieties	
Nitrogen Fixation	
Quick Propogation through Tissue Culture	
Improvements in Animal Health and Productivity	

Source: Government of India, Department of Science and Technology, National Biotechnology Board, *Long Term Plan for Biotechnology in India*, New Delhi: The Department, April 1983, p. 14.

through somatic embryogenesis *in vitro*. Currently work on perfecting *in vitro* technology is being implemented at the Central Plantation Crops Research Institute, Kasaragod; National Chemical Laboratory (NCL), Pune; and Jawaharlal Nehru University, New Delhi. A major S & T project on cattle herd improvement for improved productivity through Embryo Transfer Technology (ETT) has been taken up for implementation by DBT involving several institutions such as National Dairy Development Board, National Institute of Immunology, National Dairy Research Institute, Indian Veterinary Research Institute, and Indian Agricultural Research Institute. In addition, a project on Development and Production of Immunodiagnostic kits and another for development of contraceptive vaccines using immunological approaches have been taken up at the National Institute of Immunology.[19]

Besides the above programmes initiated under the framework of DBT, ICAR is setting up three biotechnology centres to work on the livestock and crop improvement in the country at National Dairy Research Institute, Karnal; Indian Veterinary Research Institute, Izatnagar, and Indian Agricultural Research Institute.[20]

The industrial policy of the Government has also responded to the emerging developments in biotechnology. The production of hybrid and high yielding varieties based on high and sophisticated technology have been included in the appendix I of the Industrial Licensing Policy 1973 with effect from May 1986.[21] This means that MNCs and local monopoly houses can operate in this area.

International cooperation

India hosts one of the two chapters of the UNIDO's International Centre for Genetic Engineering and Biotechnology (ICGEB) for which interim facilities are being arranged by the DBT at one of the national institutes.[22] ICGEB (New Delhi chapter) is to be involved in basic research in health and agriculture relevant for developing countries and training of S & T manpower from developing countries in biotechnology.

India also hosts a CGIAR institute viz. International Crop Research Institute for the Semi-Arid Tropics (ICRISAT) at Hyderabad. ICRISAT at the moment is in the process of developing a biotechnology facility. ICRISAT is already using molecular techniques to identify virus pathogens in crops, and aflatoxins on groundnuts, and on gene transfer across sterility barriers in sorghum and groundnut.

The Research and Information System (RIS) for the Non-Aligned and Other Developing Countries based in New Delhi has undertaken a project on Biotechnology Revolution and the Third World. This project intends to examine the issues posed by the advances in biotechnology for developing countries and identifying the suitable package of strategies to meet these emerging challenges. A number of noted experts in the field are contributing to the project. Besides, India would be hosting an Intergovernmental Consultive Conference of Experts on New and High Technologies of Developing Countries during May 1988. Biotechnology will be one of the new and high technologies to be discussed at the Conference.

At the bilateral level, India has concluded R & D collaboration agreements in the area of biotechnology with a number of countries viz. USA, USSR, UK, FRG, France, Switzerland, Sweden, Japan, Vietnam and Mexico.

Biotechnology industry

Industry in India is gradually becoming aware of the potential of biotechnology for their business and are gearing themselves to enter into the field. Hindustan Lever Ltd (HLL), an Indian subsidiary of multinational Unilever has perhaps the most intensive interest in biotechnology among the businesses in India. HLL has a strong in-house R & D base active in application of new technology to agribusiness that is central to its operations. Scientists at HLL have reportedly achieved considerable success in the use of enzyme technology to produce a number of high value fine chemicals and explored producing edible quality oil and glycerine for industrial use by using genetically modified bacteria. Through protoplast fusion of two edible varieties of yeast they have been able to produce a hybrid cell capable of producing and accumulating high amounts of fats and of utilising sugar at high rates. The newly engineered species of yeast has been successfully grown in pilot fermenters and used for extracting edible fat from biomass. They were working on tissue culture for coconuts and palms and on biological nitrogen fixation. They have discovered organic compounds which greatly increase photosynthesis in plant and have succeeded in synthesizing certain pheromones (bio-insecticides).[23] HLL has commercially launched a plant growth nutrient *Paras*[24] and has got permission to produce 20,000 tonnes of hybrid and high yielding variety seeds using high technology per annum.[25]

Hoechst India Ltd, the Indian subsidiary of another multinational was testing a drug for the treatment of glaucoma produced through genetic engineering of bacterial strain. Ranbaxy, an Indian drug company is ready to go in for the production of an intermediate used in the manufacture of semi-synthetic penicillin.[26] Some other Indian companies are entering the field on the basis of technology borrowed from Western sources e.g. Orkay is teaming up with Cetus, USA, for production of biotechnology based anti/cancer drugs.[27] United Brewaries is entering the field of diagnostics, hormones and other chemicals.[28] Southern Petrochemicals Industries Corporation (SPIC) was setting up an R & D centre to develop the process know-how for drugs of known structure and was collaborating with Cytozyme, USA, for marketing of a plant growth stimulant.[29] Some companies involved in breweries were introdocing energy saving methods of alcohol fermentation and distillation using new yeast strains e.g. DCM in collaboration with a Japanese firm.[30] A joint venture between Beardsell of Madras and Satec Ltd. UK is to introduce new biotechnology In industrial waste treatment in India particularly aerobic fermentation of strong wastes to produce single cell proteins.[31] Tatas have set up a joint venture Plantech in Singapore with Native Plants International, US, to develop new strains of plantation crops such as tea and oil palm through tissue culture.[32] TOMCO (Tata Oil) is producing fats from molasses.[33] Tata Energy Research Institute has set up a biotechnology laboratory.[34] Hindustan Insecticides Ltd, a public sector firm, was involved in development of microbial insecticides in cooperation with DBT.[35] Five multinationals viz. Seedtec International, Cargil Inc., Dehlgien Inc., Northrup King and Sandoz (through their local subsidiary) have been shortlisted by the Indian government for production of hybrid seeds in collaboration with Indian companies.[36] To tap the availability of cheap and compe-

tent skilled S & T personnel in India a few MNCs like Astra AB., Sweden are setting up biotechnology R & D centres in India.[37]

Concluding remarks

The above discussion has shown that advances in biotechnology research provide vast potential for development of a country like India. With its already well developed S & T infrastructure, availability of trained manpower, rich genetic heritage, diversified industrial base and low research costs, India is uniquely placed among developing countries to tap the potential of biotechnology. The Indian government has recognised the importance of biotechnology in its development plans and policy and has taken a number of steps to develop infrastructure and to train manpower in the field. A number of R & D projectss have been initiated. A number of firms have also started to gear themselves to apply biotechnology based processes into their business and into manufacture of biotechnology based products.

Despite so many developments, however, the application of biotechnology have yet to make a perceptible impact on the economic life in the country. The implementation of the programmes in biotechnology by DBT gives the impression of spreading modest resources thinly over a wide range of activities. The total budget of DBT for 1986-87 at Rs. 235.2 million is quite small compared to large investments being made in the Western countries and the actual expenditure at Rs. 179.4 million has even fallen short of the budgetary allocation. For the year 1987-88 the budgetary allocation is higher at Rs. 409.9 million.[38] Some of the national facilities being set up by DBT are yet underequipped.[39]

The greatest opportunity for the country in biotechnology lies in reversal of brain drain. A large number of Indian scientists working in the United States and other Western countries are at the forefront of many areas of biotechnology. The Indian government should devise ways and means to attract them back. In biotechnology the distinction between basic and applied research is almost non-existent. Hence, setting up of Biotechnology Entrepreneurship Parks (on the lines of S & T Entrepreneurship Parks) may be rewarding, particularly in attracting non-resident Indian biotechnologists. Their success, however, would depend on availability of infrastructural facilities and adequate venture capital. Further, priorities of biotechnology research in India ought to be different than in the West. Like in the Western countries, the Indian biotechnology programmes appear to be dominated by health an medicinal related research. But it is in agriculture where most of the potential for the country lies. Research in agriculture is also made more important because of lack of research in the West on tropical plants. The Department of Agricultural Research being outside the Ministry of Science and Technology where DBT is located may perhaps be responsible for relatively low priority given to biotechnology in agricultural research. There is, therefore, need for galvanising ICAR into biotechnology research and its greater coordination with DBT.

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Notes

1 On impact of advances in biotechnology on exports of developing countries see, among others, Gerd Junne, "New Technologies: a threat to developing countries' exports", a paper presented at the seminar on Revolution Tecnologica y Empleo, Mexico city, November 1984. A brief survey of issues presented by biotechnology for developing countries is available in Research and Information System for the Non-aligned and Other Developing Countries, "Biotechnology Revolution and the Third World: Challenges and Policy Options," New Delhi: December 1987.
2 Cited in "Bio-Engineering: New Era for Third World" by V.S. Prabhakar in *The Hindustan Times*, 3 December 1984.
3 Professor Tarun Ghose of Indian Institute of Technology quoted in *Daily* 12 May 1986.
4 *Hindustan Times*, op. cit.
5 S. Varadarajan at the "Seminar on Productive Harnessing of Biotechnology" organised by the Union Bank of India in New Delhi, July 1987, and reported in *Commerce* Oct. 24-30, 1987 p. 13; also see P.M. Bhargava and Anita Gambhir, "The Future of Biotechnology", *Commerce*, November 26, 1983.
6 India, *Sixth Five Year Plan, 1980-85*, New Delhi, Planning Commission, p. 326.
7 See India, National Biotechnology Board, *Long Term Plan for Biotechnology in India*, New Delhi, Department of Science & Technology, April 1983, pp. 14-24.
8 *Annual Report 1984-85*, Department of Science and Technology, Govt. of India, 198-211.
9 India, *Seventh Five Year Plan* 1985-90, Vol. II, p. 376.
10 *ibid.* p. 378.
11 *ibid.* p. 379.
12 *ibid.* p. 24.
13 *ibid.* p. 382.
14 *ibid.* p. 171.
15 *Programmes in Biotechnology*, Department of Biotechnology, Govt. of India, January 1988.
16 *Annual Report, 1986-87*, Department of Bitechnology, Govt. of India.
17 *Programmes in Biotechnology*, op. cit.
18 *Annual Report*, DBT op. cit., and *Programmes in Biotechnology*, op. cit.
19 *ibid.*
20 *Economic Times*, 24 March 1985.
21 *Economic Times*, 8 November 1987.
22 *Annual Report*, DBT, op. cit.
23 Hindustan Lever Ltd. "Biotechnology and Agriculture," Speech of Chairman at the Annual General Meeting, 18 June 1985, Bombay.
24 cited in *Daily* 12 May 1986.
25 *Economic Times* 8 November 1987.
26 Cited in "Biotechnology: The Science & Business" by P.K.B. Menon, in *Economic Times* 17 April 1985.
27 *Financial Express*, 11 March 1987.
28 *Business Standard*, 24 November 1985.
29 *Economic Times*, 24 August 1985.
30 *Financial Express*, 23 November 1985.
31 *Business Standard*, 18 December 1983.
32 *Business Standard*, 24 November 1985.
33 *Economic Times*, 17 April 1985.
34 *Business Standard*, 24 November 1985.
35 *Annual Report*, DBT, op. cit.
36 *Economic Times*, 8 November 1987.
37 *Business Standard*, 19 February 1987.
38 *Annual Report*, DBT, op. cit.
39 Arun Bhattacharjee, "Biotechnology: The Sad Lack of Original Research," *Commerce*, Oct. 24-30, 1987.

search today and in the near future lies in the new biology, i.e. immunology, cell biology, molecular biology, genetics including genetic engineering, hybridoma technologies etc. Genetic engineering today represents a culmination of human creativity with great potential for human well-being especially in the tropical areas." Therefore, the plan proposed to pay special attention to this area.

Besides the area of agriculture research, the Plan document notes the importance of organising basic research programmes in the field of biotechnology as applied to agriculture and allied sectors in view of the immediate need for breaking yield barriers in the major food crops, reducing dependence on non-renewable sources of energy and developing resistance to pests and diseases in plants and animals. ICAR has developed short-term and long-term programmes in biotechnology covering molecular biology, plant tissue culture, biological nitrogen fixation, protoplast fusion, recombinant DNA technology, immunology, immunological biotechniques in reproduction and fertility, improvement of cattle buffalo, embryo transfer technology, and genetic engineering in viruses. Research on biotechnology would be organised at the three National Centres — one each in crop production, animal production and animal health, as also through agricultural universities in a few selected locations.[12]

In addition the biotechnology was to be applied for at least 3 of the 13 illustrative S & T Missions formulated by the Seventh Plan viz. Integrated (R&D) Oilseed Development Project — self sufficiency in oil seeds, control/eradication of major diseases by immunoprophylaxis, and cattle herd improvement and increased milk production through embryo transplantation technology.[13]

In the case of Industry and Minerals, however, the Plan just notes that the industrial policy should ensure the utilisation of the expertise in the public sector and also encourage involvement of the private sector for the development of "sunrise" industries such as telecommunications, computers, microelectronics, ceramic composites and *biotechnology*.[14]

Programmes and Implementation

In pursuance of the above proposals, a number of initiatives have been taken in the Seventh Plan period. On 27 February, 1986 the Indian Government announced the formation of a full-fledged Department of Biotechnology (DBT) in the Ministry of Science and Technology in place of NBTB. The DBT would be responsible for evolving integrated plans and programmes in biotechnology, identifying specific R & D programmes in biotechnology-related manufacturing, establishment of infrastructural support at the national level, initiating programmes of manpower development, manufacture and applications of recombinant and cell based vaccines, to act as an agent of the government for import of new biotechnology based process, products and technology, and for evolving bio-safety guidelines for laboratory research, production and application.[15] A Scientific Advisory Committee (SAC) consisting of members representing different S & T agencies and other eminent authorities, has also been constituted to advise the DBT.

The DBT has initiated various schemes under integrated manpower development including post-graduate and doctoral programmes in applied multi-disciplinary areas of biotechnology at 13 universities as well as a number of short-term training courses (23 between 1984-86) to reorient the existing manpower into biotechnologgy.[17] DBT is also funding the national and overseas Associateship programme to improve the quality of research personnel in the areas of genetic engineering and biotechnology in India. To build-up a R & D base and manufacturing capabilities, the DBT has started to establish national facilities for germ plasm, animal and microbial cell/tissue culture, collections etc. The National Facility on Blue Green Algae Collection has been set up at the IARI, New Delhi to collect, identify and maintain strains in viable and genetically stable conditions and make them available to other user scientists/extension workers. The National Facility for Plant Tissue Culture Repository has been set up at the National Bureau of Plant Genetic Resources, for *in vitro* cryopreservation of economically important crop species. The National Microbial Culture Collection and Gene Bank has been set up at the Institute of Microbial Technology, Chandigarh, and the National Animal Cell/Tissue Culture Facilities have been created at the University of Poona. Three regional Animal House Facilities at the National Institute of Nutrition, Hyderabad; Central Drug Research Institute, Lucknow, and at the Indian Institute of Science, Bangalore. A National Biochemical Engineering Research Centre and Pilot Plant for scaling up biotechnological processes developed in laboratories is being established at the Institute of Microbial Technology, Chandigarh. Recognizing the vital role of synthetic oligonucleotides in biotechnology research, infrastructural facilities for synthesis and application of oligonucleotides at four centres viz. Indian Institute of Science, Bangalore, CSIR Centre for Biochemicals, Delhi; Department of Chemistry, University of Delhi, and Centre for Cellular annd Molecular Biology, Hyderabad. Capability to manufacture indigenously some of the restriction enzymes, ligases, vectors and fine chemicals which are vital inputs for research in molecular biology and genetic engineering has been developed at the CSIR Centre for Biochemicals (CFB). CFB and Bhabha Atomic Research Centre (BARC) are also importing and distributing a number of other essential chemicals and reagents not readily available. DBT is also setting up a distributed Biotechnology Information System (BTIS) to provide to scientists a quick access to published information in different major areas of biotechnology research.[18]

DBT has also started funding specific R & D projects with biotechnology application. It has sponsored a project on Bamboo Propagation by Tissue Culture at the University of Delhi developing and standardising methodologies for rapid multiplication of bamboo. Another project has been sponsored on development and production of bacterial larvaecide (Microbial Insecticide) for controlling Malaria and Filaria involving researches at a university and in insecticide companies. A project on developing biohydrometallurgical process for copper leaching has also been initiated. Of the Seventh Plan Technology Missions' DBT is involved in Missions on vaccines, Edible Oils, and the one on Cattle Herd Improvement. DBT is reportedly taking steps to build up a strong national capability and international competence in the area of vaccinology as a part of the Mission. In the case of edible oils it is planned to raise genetically identical clones of high yielding types of coconut and oil palm

Table 2 - Biotechnology Activities with Time Horizon in Different Sector in India

Time Target	Project Initiation	Activities
		Health
3 Years 1985-86	Immediate	1. Production of established viral vaccines but using new methods of tissue culture. 2. Hybridoma based monoclonal antibodies as diagnostic agents and tools. 3. Production of genetically-engineered insulin and interferon.
5 Years 1987-88	1983-84	1. Production of variety of peptide hormones, amino acids and enzymes. 2. Production of a host of viral and subunit antigens and antibodies. 3. Passive immunization for pregnancy termination. 4. Treatment of certain genetic disease. Kits for tissue matching for grafting, etc. 5. New drug delivery systems for hormonal regulations and cancer treatment. 6. Polyvalent subunit vaccines and eradication of several infectious diseases. 7. Vaccines against hepatitis.
10 Years 1993-94	1983-84 and later	1. Highly effective safe and reversible vaccines for contraception in female and male. 2. Vaccines against leprosy, malaria, amoebiasis, helminth infestations, filariasis. 3. Vacine and hormonal treatment against several cancers such as leukemia, breast cancer, and other soft tissue cancers. 4. Tissue and subcellular targetting of drugs.
Beyond 10 Years	1983-84 and later	1. Gene preparations against diseases such as sickle cell anemia, thallasemia, hemophilia, diabetes, PKU.
		Agriculture
Time Target	**Project Initiation**	**Activities**
3 to 5 Years 1987-88	Strengthen on-going projects, and initiate new work immediately	1. Large scale production of suitable rhizobial strains for soil inoculations and seed treatment in the case of various legume crops. The strains must be tested and certified for various soil, climatic and crop conditions. 2. Making available suitable strains of blue green algae and *Azolla* for different climatic and soil condition of wet land graduated cultivation. 3. Development of soil inoculation packages of *Azotobacter* and a variety of other non-symbiotic nitrogen fixers. 4. Development of production and application technology of *B. Thurintiensis* and *B. Sphaericus* for the biological control of insect pests of crops and mosquito.
5 to 10 Years 1993-94	Strengthen on-going work and initiate new work	1. Development of multi-infective rhizobial strain for inducing nodulation in a variety of leguminous and non-leguminous plants. 2. Development of reotfibre adhering ability to non-symbiotics nitrogen fixing bacteria. 3. Development of disease resistance and stress tolerance varieties of crops using tissue culture and somatic hybridization and selection technologies. 4. Improving the nutrition, quality and flavor of food grains and plants through gene cloning. 5. Rapid propagation of high yielding vegetables and fruits and fast growing elite trees.
		Industry
Time Target	**Project Initiation**	**Activities**
3 Years 1985-86	Immediate	1. Improve currently used industrial strains to international levels of productivity (antibiotics, organic acids, vitamins amino acids, etc.) 2. Introduce yeast strains in alcohol industry to yield 12-16% ethanol from molasses. 3. Improve bioreactor designs to save energy, and improve yields. Introduce better fermentation monitoring and control and end product recovery. Introduce waste conversion, utillzation and recycling. Whereever possible introduce biogas generation, production of fuel and reducing pollution. 4. Improve indigenous fermentation techniques such as coconut and jute retting, food and fuel processing, etc. 5. Set up units for new products such as various hormones, enzymes, amino acids, vitamins and biofuels, etc., using new techniques of cell cultures and bioreactors. 6. Establish units for blood fractionation by products biologically produced plasma extender, etc.
5 Years to 10 Years 1987-88 1992-93	1983-84 and later	1. Production of several new biological products, such as vaccines, hormones, amino acids, vitamins, pesticides, sweeteners, and a host of organic chemicals and drugs produced primarily through techniques of genetically engineered and fused cells of microbial, animal and plant origin. 2. Industrial exploitation of yeast and other genetically tailored organisms for the utilization of cellulose, hemicellulose and lignin for producing a variety of biofuels, chemicals and protein and fat as food and fuel. 3. Develop decentralized industrial base for conversion and utilization of woody plants and other biomass from energy plantations and social forestry for producing fuel, chemicals, food and materials. 4. Produce portable and field usable diagnostic and treatment kits for detection and treatment of a variety of metabolic and pathogenic diseases of man and animals.
Beyond 10 Years		1. Industry through investment and management should be ready to exploit the extraordinary new developments coming out of modern genetics and biotechnology.

Source: Government of India, Department of Science and Technology, National Biotechnology Board, *Long Term Plan for Biotechnology in India*, New Delhi: The Department, April 1983, pp. 22-24.

NEW CONTRACEPTIVE TECHNOLOGIES: LONG-ACTING AND PROVIDER DEPENDENT

by Anita Hardon
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Contraceptive researchers have over the past decade been developing a number of new contraceptive technology that all meet the criteria of being long-acting and supposedly easy to administer. Examples of these technologies are hormone releasing IUD's, implants and more recently contraceptive vaccines. These technologies are meant to increase the effectiveness of family planning programmes: because they are long-acting and easy to administer less user and provider failure is expected to occur. In this article I will view these methods from a women's perspective and raise some questions on the appropriateness of the developments. I will discuss in some detail the latest development: contraceptive vaccines.

Problems with these new contraceptive technologies are related to manner in which they are provided to women in health care settings and their 'medical' safety. Most of the methods mentioned above are 'provider dependent'. Women depend on providers to have them administered and in the case of implants and IUD's also to have them taken out. They can be abused in situations in which providers do not give women free choice out of the available contraceptive methods (in coercive family planning programmes, and in psychiatric institutions for example), and for this reason many women and health groups have opposed the introduction and marketing of the methods. Some safety issues of these drugs, for example the effect on the unborn child (if a woman accidently does become pregnant) and the long term effects remain unresolved. Women are very aware of the common side effects of hormonal methods, such as headache, menstrual disorders and weight changes. These side effects are however not taken serious in clinical research on the safety and efficacy of these methods. In fact some of these so called side effects are in fact inherent to the mode of action of the method. Long-acting hormonal implants such as Norplant for example are known to cause menstrual disorders because the menstrual cycle is disrupted. This can lead to amenorrhoea (lack of menstruation), spotting and excessive bleeding. Studies show that 60% of the Norplant users suffer from such disorders. The long term effects of this disruption of the menstrual cycle are not known, nor are immediate effects on libido and general wellbeing of women studied systematically.

Women need to know about what is not known about the contraceptives that they are taking. Contraceptive researchers tend to be complacent, arguing that if it's risks have not been proven, then the drug is probably safe. The risk of breast cancer due to the use of hormonal contraceptives has for example only recently become a concern. Before researchers affirmed that the risk was unproved and that the pill in fact was shown to have a 'protective effect' against breast cancer. The use of the term protective effects by contraceptive researchers reflects the complacency of researchers. The term suggests that contraceptives can be used to protect a woman against certain disorders. This is not appropriate, as the drugs simultaneously increase the risk of other disorders. They should be used for contraceptive purposes not as a preventive measure against all kinds of reproductive and other disorders.

Recently researchers are promoting contraceptive vaccines as a safer alternative to hormonal contraceptives. During a WHO Symposium on the

Safety and Efficacy of Vaccines to Regulate Fertility in June 1989 one researcher commented: with hormones we are sitting on time bomb.. there is an urgent need for a safer alternative that has a different mode of action. A number of vaccines are being developed however only one is expected to come on the market within the next decade: the so called anti-HCG vaccine.

When injected with the HCG vaccine a woman develops antibodies against HCG, a hormone (human chorionic gonadotropin) which is produced after fertilization of the female ovum. The vaccine thus inhibits further development of pregnancy, and the woman menstruates. It will take at least five years for these methods to be marketed, but already it is clear that these methods will have a number of worrying disadvantages, related to both the safety of the methods and the requirements (diagnostic tests and use of other methods before they are effective) for proper use. With respect to safety it is important to know that with this vaccine antibodies against a 'natural hormone' are induced. Because of this serious immunological disorders can potentially occur (this will be explained in more detail below). In order to provoce an immune reaction against a 'self hormone' a part of the hormone is linked to a tetanus toxoid carrier (TT carrier, also used in other vaccines). The method is temporarily irreversible (till all antibodies against HCG are secreted). If side effects occur within the period of efficacy the effect of the drug cannot be 'switched off'. The effect of the contraceptive vaccines on the offspring - if the woman becomes pregnant or is pregnant when given the vaccine - is unknown. The HCG vaccine may work as an abortifacient (by neutralizing the effect of HCG). If it does not the antibodies are likely to react with the fertilized ovum (that is producing HCG). Researchers agree that if the woman is pregnant while using the vaccine, she should be advised to abort the child.

With respect to the requirements for the use of the vaccine it is important to note that because of individual variations in immune responde the length of efficacy (aimed at being 18 months) cannot be ensured. In fact diagnostic tests (to determine the level of antibodies against HCG) are probably needed to define when the vaccine is no longer effective. The vaccines that are being developed at present have a so called 'lag period' before they are effective. This means that in the non-effective period women still need to use another method. Although the contraceptive researchers promote the vaccines as easy to administer (as injection) in reality this will probably not be the case. Vaccine use will need to be accompanied by the use of other methods and diagnostic tests.

The researchers justify the development of these (temporarily) irreversible methods by referring to the need for new contraceptives, the ease of administration of vaccines and the continuing population growth, especially in Third World countries.

In India the government's five year development plan already mentions the future introduction of vaccines into the family planning programmes and the Indian Council for Medical Research has give top priority into immunological research in contraception. Clinical trials were started fifteen years ago when an Indian researcher (Dr. Talwar) eager to test the principle of antibody reaction against HCG in human beings vaccinated six unsterilized women. Two became pregnant. The vaccine developed by the Indian Council for Medical research provoces an antibody response to one of the two chains (the so called B-subunit) of the HCG hormone. The problem is that some of the chemical components on this subunit also occur in other natural occurring hormones, such as LH (luteinizing hormone). HCG is only present during early pregnancy, but LH is one of the hormones that controls the menstrual cycle. Serious immunological and hormonal disorders could occurr if the

vaccines also reacts against LH. For this reason some scientists believe that the vaccine developed in India is not appropriate. The Indian researchers however stress that in their trials no such immunological and hormonal disorders (notably no changes in menstrual patterns) were observed, and that though in theory the disorders may occur in practice it does not happen. Soon 2nd and 3rd phase clinical trials (covering at least 200 women users) will start in India. It seems unethical to start these larger trials on unsterilized women, when the risk of serious immunological disorders - theoretically - exists. Women who participate in these trials should at least be warned on this issue.

The World Health Organisation Special Programme of Human Reproduction has promoted the development of a vaccine that induces an antibody reaction against a smaller synthetically produced segment of the HCG hormone. This segment does not appear on the LH hormone and there is thus less risk for so called crossreactivity. The vaccine has been tested in 30 surgically sterilized women and was shown to produce 'contraceptive levels of antibodies' according to the researchers (the australian Jones et. al.). The WHO intends to start 2nd and 3rd phase trials in fertile women soon to test safety and efficacy. The problem with this preparation is however that it is not suitable for marketing as it only works for a 6 weeks period. The researchers acknowledge this, but point out that it will take time to develop a preparation that works for 18 months (the period of efficacy that the researchers aim at). The WEMOS women and pharmaceuticals group believes that it is unethical to start trials on women with a vaccine which is not suitable for marketing because of it's limited period of efficacy.

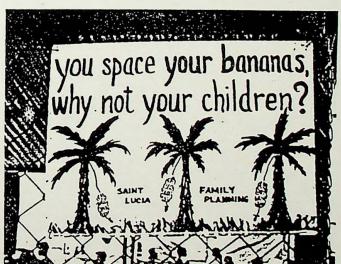
The vaccine researchers doubt whether women in industrialized countries will see the advantages of these methods, apparently directing their new technology towards Third World women, whereas in most health care setting in Third World countries side effects and proper use of these new technologies will be hard to monitor. The WEMOS women and Pharmaceuticals network believes that drugs which are not approved in industrialized countries should not be exported to Third World countries.

Researchers increasingly point at the need to test new contraceptive technologies in women in an early stage, because animal experiments have little predictive value. The early vaccine trials in India and the premature trials promoted by the WHO are examples of this. Clinical trials should only be conducted if the new contraceptive technology offers significant advantages over already existing methods. The trials that the Indian scientists intend to perform and the WHO trials on a short-acting vaccines do not meet this criterium. Likewise regulatory authorities should only approve new methods if they provide women with a safe and effective alternative to existing methods. The safety and use of a new contraceptive technology should be monitored rigorously in post marketing surveillance and an informed consent procedure should be developed for women who intend to use the new technology.

The WEMOS women and pharmaceuticals network believes that women and health organisations should be involved in discussions on the risks and benefits, and potential abuse of new contraceptive technologies in an early stage. Mechanisms for dialogue with research institutions need to be established. Concerted action against undesirable technologies is needed. These technologies can be undesirable because of medical risks, because safer alternatives exist, and because of widescale abuse of the drugs. WEMOS will monitor closely the development of new long-acting hormonal methods. Soon an information leaflet on the vaccines will be prepared and a book on the safety and problems in the use of long-acting hormonal methods in developing countries, based on a recent

consultation with women and health groups from Thailand, India, Bangladesh, Brazil and Indonesia. WEMOS also intends to stimulate discussion and research on the types of contraceptives that women do desire (for example a method to measure ovulation, or a male contraceptive), as a guidance for contraceptive researchers. With respect to this last point it is interesting that the above mentioned vaccine researchers are looking into the possibility of developing an anti-sperm vaccine. However according to them it is safest if this vaccine is given to women. In males this vaccines would be more dangerous as it produces antibodies against a natural body tissue (sperm). In women the sperm is only present 'transiently'. Perhaps the researchers also worry that there will not be enough men interested in participating in a trial for such a vaccine, and industries may doubt the potential market for such a drug. It seems unlikely that a male vaccine will be developed.

(From: WEMOS, 'Bevolkingsbeleid en het welbevinden van vrouwen: een wankel evenwicht', 6 Nov.1989, Amsterdam)



(Taken from Wechselwirkung, no.41, May 1989, a journal from Switzerland - the picture is a reproduction of a poster put up on an West Indian island)

C sers yes to hormone-based contraceptives

THE STATESMAN, 18TH MAY 94

From RAVI R. PRASAD

BELGAUM (Karnataka), May 17. — Inspite of misgivings over hormone-based contraceptives and protests by women's organizations against the introduction of these new birth control measures, the Indian Council of Medical Research (ICMR) is continuing with Phase-III trials of Norplant-1 at 10 centres in the country and heading towards a success.

The Human Reproduction Research Centre here, one of the 10, has been very successful in popularizing this new birth control measure and women using the contraceptive say they are satisfied with it.

A significant number of women have opted for Norplant-1, which is effective for five years, instead of conventional methods being offered to them at the civil hospital. The injectible contraceptives, Depo Provera and Net En, are likely to be introduced here shortly and doctors hope that these will also be widely accepted by women despite the doubts and furore created by voluntary organizations.

Contrary to the claims of several women health advocates and social workers — who are opposed to the introduction of hormone-based contraceptives in the country — women who have been using Norplant-1 asserted that they neither had any problems nor had they suffered from any complications after the contraceptive was implanted in their arm.

The ICMR itself has listed a number of side effects in the circular issued to the HRRCs about the phase III trials of Norplant-1 and instructed that the contraceptive should be removed from the woman's body in case of any complication. But so far the HRRC here has not come across any serious side effect. In one case it was removed as the women gained three kg of weight in three months.

Of the 12 women who have opted for Norplant-1, not a single one complained of any serious side-effects. Rather, they claim to be satisfied with the contraceptive and were willing to continue as a part of the ICMR's experiment despite protests made by women's organizations at New Delhi a few days back.

"We have been told about the side effects and also the aim of the experiment being conducted by the doctors. We have not been kept in the dark and made guinea pigs for the trials," says Mrs Saudhya. Vijay Tamuche, who chose to use Norplant-1 after HRRC officials briefed her about the new contraceptive.

Mrs Tamuche said the doctors had told her about the side effects but so far she had not experienced any serious problem. She opted for Norplant-1 because she had developed a complication while using a conventional contraceptive. "Copper T gave me trouble and when I consulted the doctors they told me about Norplant. So I decided to become a part of this experiment," she told **The Statesman.**

Mrs Shakira switched over from oral pills to Norplant as she had problems with the tablets. "I was told about the complications that can be caused by Norplant before I opted for it. Now I sometimes feel dizzy and my hair has started falling. Doctors had told me that this could happen and will be there for a year so I am not much worried about it," she said.

Phase-III trials of Norplant-1 will last for seven years and any decision regarding the adoption of this contraceptive in the family welfare policy will be taken only if the trial concludes successfully without any negative results. Prof B.S. Kodkany, head of the department, Gynaecology, JLN medical College and Chief Investigator of the HRRC, said.

"We are not pushing Norplant. There is no fixed target. Women are advised about the various birth control methods when they come to the hospital. They are offered a complete range of contraceptives like tubectomy, IUD, Oral Pills, etc. and they have to choose. All those who come to the HRRC have to sign a 'Informed consent form' after choosing the contraceptive, whether it is Norplant or pills," he said.

Out of 515 women who were advised by the HRRC about the contraceptives, only 13 opted for Norplant, a major success considering its recent introduction and the negative propo-

(Continued on page 9 col. 3)

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ganda about hormone-based contraceptives. A total of 186 chose Copper-T, 96 decided in favour of tubectomy and 42 wanted oral pills, according to Dr Kodkany.

Refuting the argument of women health advocates that hormone-based contraceptives like Depo provera, Net En and Norplant-1 should not be used because these need immediate medical help in case of complications, Dr Kodkany said none of these contraceptives cause any major problem. "Oral pills are also hormonal contraceptives, complications caused by these are the same as those of the new ones. Like a women discontinues pills if she has problems, Norplant can also be removed," he said.

"As far as the need of a doctor in concerned even insertion and removal of Copper-T requires minor surgery. In case of Norplant a small incision is made on the left upper arm of the women and the six capsules are inserted through the incision. The contraceptive is effective for a period of five years. These capsules are removed after this period and if the woman wants it, fresh capsules can be implanted, Dr Kodkany said.

Dr Kodkany said the HRRC had not come across any serious problem among the women who had chosen Norplant-2, the first version of this contraceptive, when it was tried out in 1986. One of those women, Mrs Jahirebi, has volunteered to become a part of this experiment. She had disappeared after 1986 and came back last month when she came to know about Norplant-1. The two capsules of Norplant-2 which were inserted in her left arm eight years back were removed early this month and she had no complaints.

During the trials, each of the 12 women who have opted for Norplant have to report to hospital one week after the insertion is done and then after a month. Then, she has to come to hospital every three months for one year and, later, twice a year for a thorough check-up. "This gives us an opportunity to test the woman for other problems also, besides looking for the side effects of Norplant," Dr Geetha Pangi, a research officer at the HRRC, said.

Interestingly, while women's organizations have been raising a hue and cry against Norplant and other hormone-based contraceptives all over the country and at New Delhi, their counterparts in Belgaum have been closely working with the HRRC here. So far no protest has been held against the trials and the office bearers of these organizations have been given a detailed explanation

Users' yes to hormone-based contraceptives

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Contrary to the claims of several women health advocates and social workers — who are opposed to the introduction of hormone-based contraceptives in the country — women who have been using Norplant-1 asserted that they neither had any problems nor had they suffered from any complications after the contraceptive was implanted in their arm.

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Of the 12 women who have opted for Norplant-1, not a single one complained of any serious side-effects. Rather, they claim to be satisfied with the contraceptive and were willing to continue as a part of the ICMR's experiment despite protests made by women's organizations at New Delhi a few days back.

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During the trials, each of the 12 women who have opted for Norplant have to report to hospital one week after the insertion is done and then after a month. Then, she has to come to hospital every three months for one year and, later, twice a year for a thorough check-up. "This gives us an opportunity to test the woman for other problems also, besides looking for the side effects of Norplant," Dr Geetha Pangi, a research officer at the HRRC, said.

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WH 3-18

Indian Express 5/12/90

Reversible vaccine for birth control soon

Express News Service

New Delhi, Dec. 4: A safe and reversible vaccine for birth control among human beings could soon be a reality, if the crucial clinical trials now under way in the country prove successful.

The vaccine, heterospecies dimer (HSD), for women, developed by scientists at the National Institute for Immunology (NII), here, has already passed the first stage of the trials, both in India and abroad. Tentative results from the second stage of trials, in which 180 fertile women are involved, are expected to be out by next March.

The studies are being undertaken at the Post-graduate Institute of Medical Education and Research, Chandigarh, All-India Institute of Medical Sciences and the Safdarjung Hospital, New Delhi. In the trials which began in August, 51 women with proven fertility and having at least two children, have been enrolled, and 130 more are to be added in due course.

NO SIDE-EFFECTS

During the first stage of the trials, conducted on 140 sterile women in India, Sweden, Finland and some other countries, the vaccine has proved that it can iduce the formation of antibodies against the pregnancy hormone and is completely free from side-effects. Based on the results of the trials, involving two different formulations, the scientists have chosen a formulation consisting of heterospecies dimer, linked to either tetanus toxoid or diphtheria.

According to Dr. G. P. Talwar, director of NII, who has played a leading role in developing the vaccine, the effect of the vaccine has already been estabiished among monkeys and baboons. The phase I trials (on human beings) have cleared the safety of the vaccine and its reversibility. The phase II trials will determine if immunisation can indeed prevent pregnancy and provide information on the threshold level of antibodies required to do so.

The injection, as a method of family planning, has several attractive propositions in that it will require only a periodic intake, with the effect lasting one or two years, and it will be free from "user failure" risk.

Another vaccine designed at the institute induces antibodies against LHRH, a key hormone made in an area of the brain, which regulates the production of gametes and sex steroids in both the male and female. The vaccine is therefore usable by both sexes. The vaccine is intended to be used for therapeutic and preventive purposes, akin to "immunological surgery".

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Call for ban on

Pros and Cons of
Contraceptives Available in India

A range of contraceptives are now available in India, particularly for women. Some of these methods are being actively propagated by the Family Planning Programme in India. Many of them are at the centre of raging controversy and debate, especially as they are being questioned by health activists and women's groups across the country.

CONTRACEPTIVES FOR MEN

Methods	Advantages	Disadvantages
1. **Coitus Interruptus** involves withdrawal of the penis before ejaculation during sexual intercourse. This method has been advocated by religious groups which do not favour contraception.	• Certain level of maturity and understanding is needed on the part of the sexual partners. The man's role and responsibility in reproduction becomes important.	• Not always possible to accurately decide the time of withdrawal or exercise enough self-control. Even a small secretion of semen contains lakhs of sperms. Therefore this method is not fool-proof.
2. **Condoms** have been in use by men for hundreds of years — originally as ornaments, then as a means to prevent sexually transmitted diseases. It is only more recently that its use as a contraceptive has been recognised and propagated. Today latex condoms are available in different textures and colours.	• Easily available • Simple to use • Success rate of about 90 per cent when used properly • No harmful side-effects	• Ignorance about our own bodies and our reproductive systems leads to improper usage • Poor quality of condoms can cause failure • Men often feel it comes in the way of complete fulfilment • Its use requires the full co- operation of the male partners, which is not always available.
3. **Sterilisation** (Vasectomy) involves a simple surgical procedure, under local anaesthesia, to remove part or all of the vas deferens, the duct which transports sperm from the testes.	• Does not require hospitalization • Does not have any adverse effect on the person's health or even libido (contrary to popular myth) • Encourages men to play a responsible role in family planning • A one-time method which gives complete protection. In the first three months after the operation, some other form of contraception should be used as well. • Chances of infections following surgery are very rare.	• Irreversible • Still not socially accepted as an effective method of birth control • Blood clots that form after surgery may cause pain and hardening of the area. However, a simple surgery can remove these painful nodules.

CONTRACEPTIVES FOR WOMEN

Methods	Advantages	Disadvantages
REVERSIBLE		
1. **Intrauterine devices (IUDs)**	• Temporary and reversible, useful in spacing children	• It is provider-controlled, as it needs to be inserted and removed by trained medical professionals
a. **The Copper-T** is so-called because it resembles the English alphabet 'T'. It is made up of a 200 mm copper wire shaped spirally, with a T-shape on top. b. The **Loop** is an S-shaped copper wire and its functions are much the same as copper-T. IUDs are positioned in the uterus. The copper content in them destroy the sperms and thus prevent conception.	• Does not interfere with the sexual act • High success rate, if positioned properly in the uterus	• It can get dislodged from its correct position, thus causing unwanted pregnancies, haemorrhage, etc. • It leads to heavy/extended menstrual periods, something which adversely effects already anaemic women • Often there are complaints of chronic back pain • It is likely to lead to pelvic infections, or intensify already existing infections (this is especially significant as almost 50 per cent of Indian women have been found to suffer from some form of reproductive tract infection).
2. **Hormonal contraceptives** a. **The oral pill** acts to introduce the hormone estrogen into the woman's body. This prevents the ova from maturing and thus prevents conception. The pill is available in various forms. Some contain both estrogen and progestin, some have only progestin and some come in the form of separate estrogen and progestin pills, administered in sequence during each menstrual cycle.	• No interference during coitus • Reversible	**Its adverse effects may be overt or less obvious, and include** • Disturbances in the menstrual cycle, usually heavy bleeding/irregular periods • Mental depression • Migraine headaches, associated with heavy blood loss • Vaginal and urinary tract infections • Blood pressure • Weakening of the immune system, exposing women to various common infections • Sterility • Ovarian cysts • Skin allergies • Malfunctioning of the liver, jaundice • Pregnancy may occur if even one dose is missed • May be difficult for illiterate women to keep track of menstrual cycle.

Methods	Advantages	Disadvantages
b. **Injectables** The hormone progestin is injected in doses of 200 mg. and is effective for three to six months. The two currently available injectable contraceptives come under the brand names Depo Provera and Norigest (Net-En).	• Long acting • High success rate	• Creates hormonal imbalances • Causes menstrual irregularities, including amenorrhoea, excessive bleeding and spotting • Chances of breast-fed infants receiving a small percentage of the maternal dose • Not reversible until the period of efficacy is complete • Full-fledged studies on all possible side-effects have not been carried out • Provider-controlled method (administration and follow-up has to be done by medical professionals)
c. **Implants** Six capsules or rods, containing the hormone levenogestral, are implanted under the skin of the woman's forearm. The drug is released slowly over a period of five years. The capsules need to be removed after this.	• Long acting • High success rate	• Requires a medical professional for insertion and removal. This takes away a woman's right over her body and reproductive functions • The poor health facilities in our country are unlikely to provide proper medical care before and after insertion • Problems in removal occur when the rods have not been inserted properly • The device should be removed before the expiry period (as it could otherwise cause ectopic pregnancy, which is life-threatening) • Studies on side-effects not completed • No research to establish that fertility will return after removal • Interferes with normal body functions, including the menstrual cycle

Methods	Advantages	Disadvantages
TERMINAL 3a. **Sterilisation** (tubectomy) involves one of two surgical procedures. * Laparotomy, the older method, is done under general anaethesia, wherein the fallopian tubes are cut and the free ends sutured or cauterized. This prevents the union of ova and sperm, thus avoiding conception. * Laparoscopy involves the use of a laparoscope (a tube-shaped optical instrument which permits examination of the internal organs from outside) by which the fallopian tubes are drawn up and bound by a plastic ring, which has the same effect as laparotomy.	• A permanent and effective method for couples who have had the desired number of children	1 Sterile operating facilities are pre-requisites not readily available in our health system • Since the tubes are deep-seated, bringing them to the surface during the surgery may injure other organs. • Two incisions are made during surgery; improper care may lead to infection • Improper placement of the ring may result in ectopic pregnancy Being an irreversible method, opting for sterilisation assumes: * joint responsibility on the part of the couple * accepting it out of one's free will and not because of any pressures or compulsions * willingness to take necessary precautions/care following surgery, such as rest, medication, preventing infection, etc.

Methods	Advantages	Disadvantages
b. **Abortion** (Medical Termination of Pregnancy, MTP) The various methods for induc- ing abortion are: * Suction * Dilatation and curettage (D&C) * Combination of the above * Induced abortion (injection and abortifacients) * Surgical removal The method used depends on the stage of pregnancy. Suction or D&C are preferred in the initial (upto 16) weeks; methods 4 and 5 are used between 16 to 24 weeks.	• MTP can be used to terminate an unwanted or unplanned pregnancy	• Chances of infection in the vagina, cervix or buttocks. If unattended, this may result in sterility in the woman. • Chances of excessive blood loss, leading to anaemia • Possibility of injury during the process of D & C • Improper removal of the embryo from the uterus may lead to toxicity, often fatal to the mother • Due to lack of trained personnel, or proper hospital facilities, often dangerous and unscientific methods are used. This should be avoided at all costs.
c. **The abortion pill** Mifepristone, commonly known as the French Abortion Pill, consists of the chemical compound, RU 486. It needs to be administered along with a small dose of prostaglandin. This increases the frequency and strength of the uterine contractions needed to expel the embryo.	• Effective in the early weeks of pregnancy • Surgical procedures are avoided	• Possibility of excessive blood loss leading to anaemia • Requires medical attention and follow-up, which is not possible given the poor medical infrastructure in our country • This is still under trial, with neither the government nor the scientific community taking responsibility to inform women about the method, its proper use and impact. • Is effective only when administered in the first 7 or 8 weeks of pregnancy.

Translated from Hindi by Nargis Sanjivini Satyapal, from the book 'Prajanan Niyantran Ki Koshishen — Samwad Ke Prayas', written by three women activists in Bombay — Chayanika, Swathija and Kamakshi.

'Prajanan Niyantran Ki Koshishen — Samwad Ke Prayas', a joint venture by three women activists in Bombay — Chayanika, Swathija and Kamakshi — explains very clearly the meaning of *Prajanan* (reproduction/procreation) and the efforts being made to control it, as the title suggests. This work is an excellent effort, especially towards portrayal of the social and political pressures under which it is mostly the women who have to adopt some of the various birth control methods. The book deals at length with both merits and demerits of each contraceptive method as well.

Results

Antibodies to hCG

Amongst the initial thirty subjects entering the trial, there was laboratory and clinical evidence that ten had received an unstable vaccine emulsion at at least one injection. These women were replaced by new subjects who received vaccine of stability consistent with that administered to the remainder of the subjects.

All subjects who received the complete vaccine in a stable emulsion acquired antibodies to hCG as assessed by a semiquantitative radiobinding method (table II, fig 1). According to our calculation that an antibody binding level of 0·52 nmol/l might be required in peripheral blood to neutralise the physiological actions of hCG in the peri-implantation period or to mediate a cytotoxic effect on the blastocyst, a putative contraceptive effect was obtained in all subjects. The mean values in groups 1–4 attained this level by 6 weeks after the first injection (ie, at the time of the second injection) and it persisted for almost six months. In group 5, the mean value rose above the computed contraceptive threshold by the 5th week and remained above it after six months. Longer term follow-up of two subjects in group 5 has indicated the persistence of a contraceptive antibody level for 9 and 10 months.

In selected sera with relatively high peak antibody levels the two methods of quantitative analysis, direct binding and Scatchard analysis, were compared for both hCG and hCG-β 109–145. Examples are shown in table III.

Antibodies to Diphtheria Toxoid

Fig 2 shows the levels of anti-diphtheria toxoid (DT) antibody in subjects receiving the complete vaccine. All subjects had preexisting immunity to DT. The levels of anti-DT remained static in control (placebo) subjects. Amongst subjects receiving the full vaccine, twelve out of twenty showed a significant rise in antibody and the remaining eight showed no response. Three out of four subjects in group 4 and all four subjects in group 5 showed a pronounced antibody response to DT. It is noteworthy that there was no "tertiary" boosting of DT antibody response after the second injection.

Safety Aspects

No subject experienced serious trial-related adverse effects. Several women in group 5 had mild and transient

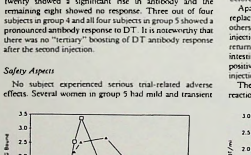

Fig 1—Mean binding levels for anti-hCG antibodies in serum for each group over study period.
Note antigen dose-related response.

TABLE III—ANTI-hCG ANTIBODY LEVELS IN 4 PEAK LEVEL SERA FROM THREE SUBJECTS TESTED BY DIRECT BINDING AND ANTIBODY DILUTION AND BY SCATCHARD ANALYSIS

Dosage group and subject no	Interval after 1st injection	Binding nmol/l	
		Direct binding	Scatchard analysis
Group 4, 19	Wk 7	1·74 (1·1–10·0)	1·90 (1·1–10·0)
Group 4, 21	Wk 7	2·30 (2·2–9·6)	1·12 (0·8–12·0)
Group 5, 30	Wk 7	4·14 (3·6–8·0)	6·19 (2·7–25·0)
Group 5, 31	Wk 8	5·90 (3·7–6·8)	8·02 (1·8–30·0)

myalgia within 48 h of the injection. This was similar to, though less pronounced than the effects seen in subjects (later replaced) who received injections in which the emulsion was unstable. There were no immediate local reactions to the injection. Two subjects reported pruritus and erythema at the injection site, one after the first injection and the other after the second injection.

Several subjects had sporadic abnormalities in blood and urine. There were isolated instances of raised plasma cortisol, but the only other endocrine abnormalities were raised follicle stimulating hormone and hLH levels in subject 28 (group 5, "placebo" injection, adjuvant and vehicle alone) who had an early menopause during the trial.

Medical disorders thought to be unrelated to the vaccine were diagnosed in five of the total of forty-three subjects initially entering the trial. They were acute cholecystitis, Wolf-Parkinson-White syndrome, iron-deficiency anaemia, acute pyelonephritis, and colonic diverticulitis.

In twenty-five of the thirty women who comprised the definitive trial subjects the menstrual pattern was unchanged. Of the other five, one (control) had an early menopause, three test subjects reported intermenstrual spotting, and one test subject had menorrhagia. There was no difference in the incidence of short cycles (< 26 days) or long cycles (> 31 days) in test and control groups either before or after vaccination.

Apart from the seven subjects who were withdrawn and replaced after receiving unstable emulsions, there were three others who were replaced after they had received their first injection. One had domestic problems; a second, recently returned from south-east Asia, had recurrence of a parasitic intestinal disorder; and a third had converted to DT skin test positive when screened before the scheduled second injection.

The details of assays for cross-reactive autoimmune reactions with pituitary hormones and with various body

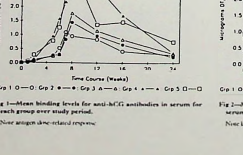

Fig 2—Mean binding levels for anti-diphtheria toxoid antibodies in serum for each group over study period.
Note lack of dose-related response.

tissues will be reported elsewhere. In summary, however, there was no evidence of reactivity with follicle stimulating hormone or hLH in any of the sera. There were minor and transient positive reactions of some sera in a routine tissue autoantibody screen. Some sera reacted with indeterminate cells in the islets of Langerhans of baboon pancreas. The meaning of these reactions is unknown.

Discussion

The anti-hCG vaccine reported here gives promise of being an acceptable means of birth control in that the target antigen is present transiently in the reproductive process, the immune response appears specific to the target hormone, and the effect is potentially reversible. Data in non-human primates indicate that, after antibody titres wane, pregnancies can be achieved without untoward consequences.* The vaccine is based on a synthetic antigen that would allow quality control and economy in large scale production. It is the first synthetic (peptide) vaccine to be developed for systemic use in man. One previous clinical trial involved the oral administration of a synthetic vaccine directed against *Escherichia coli* enterotoxin.†‡

The results indicate that, when incorporated in the existing delivery system, a small synthetic molecule such as CT 109–145 hCG-β is immunogenic and that its sustained release from an intramuscular depot maintains an antibody response for several months. The principal adverse reaction was myalgia, and the fact that this was especially pronounced in the ten women who received unstable vaccine indicates the need for completely reliable delivery systems. The reactions were presumably due to rapid release from the injection site of the water-soluble adjuvant. Data in laboratory animals suggest that the answer may lie in incorporation of a synthetic antigen such as hCG-β 109–145 into biodegradable microcapsules (Stevens V C, unpublished).

0·26 nmol/l of anti-hCG binding in vitro equates approximately to an in-vivo hCG concentration of 135 mIU/ml—a value found in the second half of a conceptional cycle. If we allow for the fact that the biological neutralising activity of the antibodies formed in response to the vaccine is about 50% of their in-vitro binding (unpublished data from WHO file), an amount of antibody capable of neutralising 270 mIU/ml of hCG in vivo might conceivably be expected to disrupt pregnancy at the peri-implantation stage. This equates to an anti-hCG antibody level of 0·52 nmol/l in the trial sera—a level attained by all subjects, and persisting for between 3 and more than 6 months in groups 4 and 5. The mean antibody levels in each of the five groups showed a dose-response pattern. Calculations will be tested when the vaccine is subjected to phase 2 clinical trials.

The antibody results for the carrier protein, diphtheria toxoid, were interesting in their lack of a dose-response effect. Most of the subjects had substantial pre-existing immunity to diphtheria. Antibody levels were boosted by the first injection in some but not all, and none had an anamnestic response after the second injection. This suggests that an escalating immune response to DT with repeated booster vaccination is unlikely to be troublesome. However, in view of the conversion of one subject to DT skin test positive after her first injection, it will be necessary to screen all individuals with this simple test before repeat vaccinations. Individual variations in the antibody response to the antigen and the carrier and the discordance between the two response patterns with different vaccine doses require further investigation—particularly with regard to possible histocompatibility type restriction of the immune reactions.

The concept of immunisation against hCG was proposed by Stevens.*§ Earlier clinical trials of a vaccine based on the whole β subunit of this hormone‖ indicated the potential of the approach to contraception but raised concerns about specificity since the subjects acquired antibodies which, although they were capable of neutralising hCG, cross-reacted with hLH.¶** Immunosafety studies of the current vaccine in baboons and in the present clinical trial revealed no such cross-reactivity and gave evidence of serological and clinical safety sufficient to justify further trials of efficacy and acceptability. This trial has also facilitated the establishment of drug-regulatory assessment criteria and clinical trial requirements for contraceptive vaccines in general and will provide an impetus to further approaches based on other target antigens in the reproductive tract such as those associated with spermatozoa and the trophoblast cell membrane.

Primary acknowledgment must be given to the innovation and commitment of the trial subjects. The support of a series of WHO Task Force associated staff and scientists over 14 years underpinned the development of the vaccine. We are also grateful to R. Elton for protocol guidance and to the Centre for Population Research of the National Institute of Child Health and Human Development of the National Institutes of Health for the generous gift of hCG (CR 121). Dr K. Forbes and Dr C. Haines provided clinical assistance in the trial. Sandoz provided financial assistance and the trial was supported by a grant from the Wiseman Medical Trust.

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BIRTH CONTROL VACCINE

Sir,—Phase 1 Clinical Trial of a World Health Organisation Birth Control Vaccine, the title of the first paper in your June 11 issue, may give the impression that the prototype vaccine described is the property of WHO. The WHO Special Programme of Research Development and Research Training in Human Reproduction fosters research in human reproduction with particular reference to developing countries, and it has been supporting the development of several methods of fertility regulation, including vaccines. This work is done in collaboration with individual investigators, academic institutions, and the pharmaceutical industry. WHO does not own or produce any of the methods of fertility regulation whose development it has supported; they remain the property of the investigators, institutions, or companies with which WHO is collaborating. Papers of this type are usually cleared through WHO channels to ensure that they do not contain information that might lead to misunderstanding, but this one was not.

World Health Organisation,
1211 Geneva, Switzerland

J. BARZELATTO

THE LANCET, AUGUST 6, 1988

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PHASE 1 CLINICAL TRIAL OF A WORLD HEALTH ORGANISATION BIRTH CONTROL VACCINE

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Summary A birth control vaccine incorporating a synthetic peptide antigen representing the aminoacid sequence 109–145 of the C-terminal region of the β subunit of human chorionic gonadotropin (hCG-β) was submitted to a phase 1 clinical trial. Thirty surgically sterilised female volunteers, divided into five equal groups for different vaccine doses, received two intramuscular injections six weeks apart. Over a six-month follow-up there were no important adverse reactions, and potentially contraceptive levels of antibodies to hCG developed in all subjects. In the highest vaccine dose group, the results gave promise of a contraceptive effect of six months' duration.

Introduction

SINCE 1974, the Task Force on Birth Control Vaccines of the World Health Organisation (WHO) Special Programme of Research, Development and Research Training in Human Reproduction has promoted the development of a contraceptive vaccine directed against the pregnancy hormone human chorionic gonadotropin (hCG). There are several possible mechanisms by which such a vaccine might exert antifertility effects. One is the stimulation of antibodies that neutralise the luteotropic action of the target hormone/antigen. This would result in regression of the corpus luteum and disruption of the peri-implantation embryo, leading to an apparently normal menstruation. Another possible action is by a direct antibody-mediated or cell-mediated cytotoxic effect on the hCG-producing cells of the peri-implantation blastocyst.

Whatever the mode of action of such a vaccine, data in the rearmouse[1] and the baboon[2] established the principle that immunity to hCG is capable of blocking fertility at an early stage of pregnancy with no discernible alterations in the menstrual cycle. This method, therefore, could be a highly acceptable birth control strategy in both developed and developing countries.[3,4]

To achieve specificity and to avoid the possibility of cross-reactive autoimmunity, particularly involving the β subunit of human luteinising hormone (hLH), the experimental vaccine was based on a synthetic oligopeptide corresponding to the aminoacid sequence 109–145 of the carboxy-terminal

TABLE I—DOSAGE SCHEDULE FOR VACCINE COMPONENTS

Group	CG peptide-carrier conjugate (μg)	Adjuvant (μg)	Vehicle (μg)
1	50	25	25
2	100	50	50
3	200	100	100
4	500	250	250
5	1000	500	500

(CT) region of the β subunit of hCG which is absent in β-hLH. Adequate immunogenicity was achieved by conjugating the antigen to diphtheria toxoid to form a hapten-carrier complex.[5] Systemic immunisation of baboons with this complex was effective in inhibiting fertility despite the fact that there is only 3–15% cross-reactivity between antibodies to the CT region of hCG-β and baboon CG.[6] Further immunogenicity studies in inbred strains of mice, and in rabbits and baboons, led to the formulation of a vaccine incorporating an adjuvant and a vehicle that was suitable for use in man.[7]

The vaccine comprises a synthetic hCG-β CT peptide 109–145, produced by the solid phase procedure of Tregear et al[8] (Peninsula Laboratories, Belmont, California), conjugated to a protein carrier, diphtheria toxoid (Connaught Laboratories, Swiftwater, Pennsylvania). The composition and purity of the peptide antigen was confirmed by high voltage electrophoresis, thin-layer chromatography, and high performance liquid chromatographic analysis. The remaining components of the vaccine were a water-soluble synthetic adjuvant, N-acetyl-glucosamine-3yl-acetyl-L-alanyl-D-isoglutamine (CGP-11637) (Ciba-Geigy, Basle) and a saline-oil emulsion vehicle (Ciba-Geigy, Basle) with an oil phase consisting of 4 parts squalene to 1 part mannide mono-oleate ("Arlacel A"), as an emulsifying agent. New conjugation methods were established to produce a highly stable peptide-carrier immunogen.[9] The diphtheria toxoid carrier was reacted with a bifunctional reagent, 6-maleimido caproic acyl N-hydroxy succunide ester (MCS) which couples to free amino groups. After purification, the modified diphtheria toxoid was reacted with the hCG-β CT peptide in a reduced state whereby the free SH on the peptide cysteine residue coupled to the maleimido group of the MCS/carrier complex. This reaction is virtually 100% effective and is very specific under the conditions adopted. The conjugate was constructed with a peptide/carrier ratio of 24–28 peptides to 10[5] Daltons carrier.

This vaccine again proved efficacious in baboons; and, after routine toxicological studies in laboratory animals and immunosafety studies in baboons,[7] drug regulatory authorities in the USA and Australia gave permission for its use in a phase 1 clinical trial for safety and immunogenicity.

This report describes the characteristics of the immune response elicited by this vaccine with particular reference to its potential efficacy and safety as a fertility regulating method.

Subjects, Materials, and Methods

The subjects consisted of thirty women aged 26–43 years who had been surgically sterilised and who gave their written and informed consent to participation in the trial. They had been screened to ensure that they were not of HLA B27 type, that they were diphtheria toxoid skin (scratch) test negative, and that they had no relevant medical illness. The subjects were numbered sequentially, disposed in 5 dosage groups of six each, and received the vaccine by deep injection into the gluteal muscle on two occasions 6 weeks apart. In each group, four subjects received the full vaccine and two (numbers 2 and 4 in each group) received the vehicle and adjuvant alone in a similar injection volume. The vaccine components were reconstituted and emulsified on the day of administration. The dosage schedule is detailed in table 1.

After initial screening examination and investigations, subjects kept a record of menstrual bleeding. Immunisations were begun after three months and subjects were monitored for six months after the initial injection. They were admitted to hospital for 48 h after each injection for clinical observation and investigations. They were also seen as outpatients for clinical assessment and laboratory testing at 1, 2, 5, 7, 8, 12, 16, and 24 weeks from the first injection.

The levels of antibodies elicited in immunised women were estimated by determining the binding of ^{125}I-labelled hCG, diphtheria toxoid (DT), and hCG peptide 109–145 to varying dilutions of sera collected at intervals after immunisation. Results were expressed as amount of antigen bound per unit volume of undiluted serum. Purified hCG (13 450 IU/mg) was obtained from the US National Institute of Child Health and Human Development as batch CR-121. The procedure for iodination has been described by Powell et al.[10]

Dilutions of pretreatment and postimmune sera were prepared in 0·01 mol/l sodium phosphate plus 0·14 mol/l sodium chloride buffer, pH 7·4 (PBS), containing 0·05 mol/l edetic acid and 20% normal calf serum (NCS). These dilutions were tested for binding to 0·26 pmol hCG or hCG-β (109–145) and to 10 ng diphtheria toxoid. Triplicate samples of 200 μl of each dilution, 100 μl of labelled antigen, and 500 μl of 1% bovine serum albumin/PBS were incubated at 4°C for 120 h before the addition of 200 μl 50% calf serum/PBS and 100 μl 25% polyethylene glycol. After centrifugation at 1500 g for 15 min, the supernatants were decanted and the precipitates were counted. The binding in preimmune sera from each woman was used to calculate nonspecific binding for hCG and peptide. Nonspecific binding for diphtheria toxoid was calculated from nonimmune rabbit sera dilutions. Because of the low binding levels observed in some sera, antigen binding was calculated by the antibody dilution method.[10] In several peak-level sera, comparative inhibition assays were done with unlabelled antigen. Inhibition plots were assessed by Scatchard analysis.[11]

A particular focus of the clinical and serological assessment of vaccine safety was evidence of cross-reactive autoimmunity. Although further reference to these aspects will be made below, details of the investigations and their results will be reported separately.

TABLE II—ANTI-hCG ANTIBODY CONCENTRATIONS IN SERA OF SUBJECTS RECEIVING COMPLETE VACCINE

Group	Mean hCG bound (nmol/l) at intervals after first injection (SE)										
	Day 1*	Day 7	Day 14	Wk 5	Wk 6†	Wk 7	Wk 8	Wk 12	Mo 4	Mo 5	Mo 6
1	0·000	0·033 (0·026)	0·026 (0·026)	0·226 (0·078)	0·521 (0·226)	1·000 (0·402)	0·948 (0·279)	0·835 (0·322)	0·413 (0·131)	0·293 (0·165)	
2	0·000	0·025 (0·013)	0·029 (0·012)	0·260 (0·115)	0·900 (0·322)	0·830 (0·192)	1·435 (0·420)	0·963 (0·347)	0·630 (0·251)	0·295 (0·073)	
3	0·000	0·022 (0·013)	0·119 (0·053)	0·229 (0·060)	0·283 (0·099)	1·013 (0·307)	1·763 (0·524)	1·140 (0·228)	0·830 (0·198)	0·330 (0·133)	
4	0·000	0·000	0·099 (0·039)	0·950 (0·173)	1·570 (0·297)	1·745 (0·144)	2·510 (0·312)	2·675 (0·257)	1·480 (0·246)	0·390 (0·152)	
5	0·000	0·058 (0·050)	0·278 (0·139)	0·783 (0·300)	1·250 (0·313)	2·531 (0·764)	3·368 (0·904)	3·358 (0·577)	1·451 (0·330)	0·750 (0·292)	

* = 1st injection, † = 2nd injection

Laboratories at the National Institute of Immunology have been working to identify potential antigens that could be used in birth control vaccines. Four approaches to achieve this have been adopted. These are 1) identification of sperm antigens capable of generating antibodies that can immobilize sperms, 2) Identification of egg-antigens that can block fertilization either by masking sperm receptor sites or by building up a physical barrier that the sperm cannot penetrate,3) Hormonal interception such as LHRH or gonadotropin releasing hormone can be intercepted to bring about cessation of the reproductive process in both males & females and 4) by neutralization of a hormone that is essential for the sustenance of pregnancy. The fourth approach is the most advanced amongst these and will be the matter of discussion in this article.

Human chorionic gonadotropin (hCG) is a hormone that is released by the fertilized egg. It acts as a signal to inform the body that conception has occurred and thereby prepares the body for pregnancy. It also prevents the degeneration of the corpus luteum thereby ensuring high levels of progesterone. Progesterone facilitates the implantation of the embryo in the uterus. The vaccine which uses only the β subunit (hCG has two, alpha and beta) generates antibodies that neutralize the hormone, thus intercepting the signal midway. The hormone subunit

is linked to a carrier molecule like tetanus toxoid thereby rendering it 'non-self' or 'foreign' and provoke the immune system. The carriers also stimulate a stronger response against these molecules.

Prof.G.P.Talwar Director, of the National Institute of Immunology and his associates first proposed the use of β-hCG linked to tetanus toxoid as a candidate birth control vaccine (BCV). Studies conducted on 65 women in five different countries had demonstrated the absence of side-effects of the vaccine. However,it also showed a variation in response to the vaccine from one individual to another ,prompting investigators to look for other formulations with better efficacy,since low antibody levels meant that the woman was not protected from pregnancy. Experiments revealed that a formulation of the alpha subunit of ovine luteinizing hormone (α-oLH) annealed to β-hCG-TT was able to elicit a greater immune response, yet had virtually no side-effects.

Phase I clinical trials employing the β-hCG vaccines were initiated in May,86 (using three formulations) on 105 volunteers at 5 centres in India. The trials demonstrated that the vaccine was well tolerated, had no adverse side-effects and generated sufficiently high levels of antibodies. The antibody level in all immunized subjects decline to near zero level by the 54th week confirming the reversibility of the vaccine. The vaccine will go sequentially upto Phase IV after

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AN INDIAN BIRTH CONTROL VACCINE

In a world survey by the Population Crisis Committee towards the end of 1986, it was revealed that 80% of the population from the developing world has inadequate access to birth control. That eventhough India spends nearly U.S.$550 millions per year on family welfare programmes, the results have not been commensurate with the investment. Bureaucratic constraints together with the emphasis on sterilization to the exclusion of other contraceptive options have resulted in only a third of couples in the reproductive age practising family planning.

A birth control vaccine (BCV) may revolutionize the family planning programme due to the following advantages:

-It will have an anti-fertility effect for a longer duration (a year or more) without the need for continuous administration of any pharmacologically active agent.

- The effect of this vaccine will be reversible. - Presently available contraceptives lead either to the alteration, inhibition or neutralization of a physiological function, very often accompanied by undesirable side-effects. Vaccines can be tailormade so as not to affect other body functions adversely.

- The vaccine employs carrier molecules to elicit an immune response which also afford prophylaxis against

other health-hazards like cholera, tetanus diphtheria etc..

- It is also suited for low-cost and easy delivery through existing health infrastructure.

- Finally, such a vaccine is expected to lend itself to large-scale synthesis and manufacture at very low cost.

It is well known that there exist a number of molecules that are essential for and highly specific to different events in the reproductive cycle eg. production and release of gametes, fertilization, development of the embryo, its implantation in the uterus, initiation & sustenance of pregnancy etc. By targeting these molecules for an 'immune-attack', the reproductive process could be impaired. By modifying these molecules the immunologist succeeds to fool the immune system into attacking these molecules which would have otherwise been spared by the immune system for being 'one of our own'. The criteria followed to select such a target molecule that would be a potential BCV is (a) one that is essential to the process of reproduction (b) which is not present in other body tissues or fluids, or if present only transiently and in very low amounts. Several such molecules or antigens have been characterized which include several reproductive hormones, several antigens of the sperm, egg antigens (zona pellucida), embryonic and foetal tissue antigens etc.

immunity, persisting for periods in excess of 12 months, can be elicited with such preparations in experimental animals. The second phase of this work is concerned with optimizing the anti-hCG vaccine to the point where it represents a safe, effective and acceptable pre-product formulation. Preliminary results indicate that the use of a combination of carefully selected and engineered hCG peptides greatly enhances the anti-hCG antibody response and that alternative carriers, adjuvants and delivery systems, offer promise in terms of producing an anti-hCG vaccine with enhanced efficacy, safety and a prolonged duration of activity following a single injection.

During the reporting period, the Task Force has implemented a new research programme to develop a vaccine directed against the trophoblast of the peri-implantation embryo. In contrast to earlier studies carried out in this area, in which classical biochemical approaches were used to isolate trophoblast membrane protein antigens of potential interest for vaccine development, the Task Force is employing monoclonal antibodies (MABs) and recently developed biotechnological procedures in order to identify, isolate, characterize and select relevant molecules more precisely. A sperm antigen classification system has also been initiated by the Task Force, using the same techniques and procedures as for the trophoblast antigen work, in an effort to standardize and rationalize the information being generated by the large number of investigators working in this area with support from other international and national funding agencies. This antigen classification project is considered by the majority of the investigators in the field to be an essential aid to vaccine development.

In preparation for these new activities, the Task Force carried out an international, multicentre collaborative project to evaluate and assess the large number of anti-trophoblast and anti-sperm MABs that were already available. A total of 111 MABs, 29 providing laboratories and 42 evaluating laboratories were involved in this project, the results of which were reviewed in a WHO-sponsored workshop held in conjunction with the sixth International Congress of Immunology in Toronto, Canada, in July 1986. As a result of these initial studies, a number of anti-trophoblast and anti-sperm MABs have been selected as reagents for the identification, isolation, characterization and selection of molecules for evaluation as components of prototype anti-trophoblast and anti-sperm vaccines.

The Task Force has continued to coordinate its research activities with other vaccine development programmes within WHO and with other international and national programmes engaged in the development of fertility regulating vaccines. This coordination has involved participation by representatives of other programmes and agencies in Steering Committee meetings of the Task Force and by Special Programme representatives in relevant meetings of other agencies.

THE RATIONALE FOR FERTILITY REGULATING VACCINE DEVELOPMENT

Although the number of fertility regulating methods currently available is probably greater now than at any time in the past, it is still not adequate to meet the widely varying cultural, religious, personal and service needs of all populations, particularly of those in the developing countries. Many of these methods act by exerting a pharmacological action at one or more points in the reproductive process, leading to the alteration or inhibition of a physiological function and resulting in an antifertility effect. This desired effect is often accompanied by less desirable side effects of varying types and intensity, which, together with the increasing concern being expressed about the sequelae of long-term use of many of these preparations, is having a major influence on their acceptability and continued use.

If vaccines could be developed which would safely and effectively inhibit fertility, without

producing unacceptable side effects, they would be an attractive addition to the present armamentarium of fertility regulating methods and would be likely to have a significant impact on family planning programmes. The theoretical advantages that a fertility regulating vaccine (FRV) would have over currently available methods of fertility regulation include: (a) lack of pharmacological activity and the often attendant side effects; (b) long-lasting action following only one or two injections; (c) administration by a procedure associated with positive health benefits; and (d) low manufacturing cost and ease of delivery within existing health services.

Essential to the development of FRVs is the identification of components of the reproductive system whose neutralization by immunological means will result in a safe, effective and acceptable antifertility effect, as well as the identification of appropriate animal models in which relevant preclinical studies of vaccine safety and efficacy can be carried out.

OPTIONS FOR FERTILITY REGULATING VACCINE DEVELOPMENT

Mammalian reproduction is a highly complex biological process involving diverse and specialized molecular systems and our knowledge of the number and type of molecules that are both specific to and essential for successful reproduction is rapidly increasing as the result of both clinical and basic research in the reproductive sciences. Immunization studies have demonstrated that many of these chemical entities, when suitably modified, are capable of eliciting an immune response which will neutralize the biological activity or destroy the structural integrity of the parent molecule, thereby reducing or inhibiting fertility in the immunized animal. Furthermore, there is a substantial body of information linking naturally occurring immunity to some of these molecules with certain types of infertility. These experiments of man and of nature indicate that there are many components of the reproductive tissues that could form the basis of antifertility immunogens for use in the development of FRVs.

Whilst virtually every step in the reproductive process is accessible to immune attack, not all represent attractive targets for FRV development. Immunization to some of these target molecules can result in a low level of antifertility efficacy and/or can produce unacceptable side effects, ranging from minor disturbances in endocrine function through to the more serious immunopathological sequelae of auto-immunity and immune-complex disease. In order to avoid these potential side effects and hazards, it is necessary to select carefully those immunogens that will produce safe, effective and acceptable antifertility effects. Ideally, such candidates for FRV development, would need to be: essential for the success of the reproductive process; accessible to immune attack; specific to the intended target and not represented in other body tissues or fluids; located in a site where a specific and controlled immune reaction will have no immunopathological or other undesirable consequences; and present only transiently or in small concentrations. These criteria are met by some molecules in the sperm membrane, the zona pellucida of the ovum, the trophoblast cell membrane of the peri-implantation blastocyst, and in the early placenta. In addition, some secreted products of these tissues, such as hCG from the trophoblast, also appear to be promising candidates. Prototype vaccines, incorporating natural and synthetic preparations based on several of these tissue-specific immunogens, have been produced and evaluated in animal and clinical studies.

CURRENT RESEARCH ON FERTILITY REGULATING VACCINES

There is currently a major interest in FRVs in many countries and several national and international agencies are funding work in this area. These studies cover virtually all aspects of basic research on the molecular events involved in gametogenesis, comparative evaluation of interactions between monoclonal antibodies, biosynthesis of antigens using recombinant DNA techniques, and clinical trials of prototype vaccine formulations.

The National Institute of Child Health and Human Development (NICHD) in Bethesda,

was formulated immediately prior to injection by dissolving the peptide-carrier conjugate and MDP in isotonic saline and subsequently mixing this aqueous component with the squalene oil, using Arlacel as the emulsifying agent. Vigorous mixing of these components is required in order to generate the high shear forces needed to achieve satisfactory emulsification.

Although no adverse side effects had been detected in the extensive preclinical toxicity, safety and efficacy studies carried out with this vaccine formulation in mice, rats, rabbits and baboons, no information had been obtained on the tolerance to, and immunogenicity of, this formulation in humans. Therefore, the principal objective of this Phase 1 clinical trial was to determine what, if any, side effects were produced by this vaccine. In addition, the levels of anti-hCG antibodies elicited by the vaccine were measured and compared to those that would be expected to confer antifertility efficacy in fertile women.

A total of 30 previously electively sterilized women volunteers were needed for the trial and recruitment was initiated in November 1985, following receipt of the necessary WHO, institutional and government approvals (Jones, 1986a-b). Telephone inquiries, requesting additional information about the trial, were received from a total of 185 potential volunteers of whom 93 were considered suitable candidates. Of these, 61 expressed an interest in taking part in the trial and 47 were subsequently selected for screening. A total of 13 women were excluded at the screening stage, for a variety of social, psychological and medical reasons, leaving the required 30 with four replacements, should these be needed.

In the interests of safety, necessitated by the novelty of the vaccine and the lack of previous clinical information with this type of formulation, the trial was conducted in a modified "dose-finding" manner in one centre. Six of the 30 women volunteers were assigned to each of the five dose groups indicated in Table 1, the highest of which, Group V, being the dose expected to elicit a level of immunity sufficient to confer antifertility efficacy, based on the results obtained in the baboon efficacy studies. Of the six women in each dose group, four received the complete vaccine and two received a "placebo" preparation consisting of the MDP adjuvant and emulsion vehicle only. Immunization was effected by two injections into the gluteal muscles at an interval of six weeks and the subjects were followed up on an in-patient and out-patient basis for a total of six months. A large number of routine and trial-specific examinations and laboratory investigations were carried out over this period.

The majority of vaccine recipients in all dose groups produced antibodies to hCG as well as to the DT carrier component of the vaccine. The anti-hCG antibody levels in Groups I, II and III exhibited only small dose-dependent increments whereas those in Groups IV and V did not follow this pattern and were much lower than Groups I-III. The only side effects considered significant by the resident physician, were transient muscle and joint pains reported by a few subjects. These symptoms, believed to be produced by the MDP component of the vaccine, were most marked in subjects in Groups IV and V but were satisfactorily controlled with analgesics and did not cause any of the volunteers to withdraw from the trial. Recovery in all cases was complete and there were no associated relevant serological abnormalities. Two subjects withdrew from the study after the first injection for reasons unrelated to the trial. A third subject was excluded after she converted to DT skin test positive following the first injection of the vaccine.

In view of these unexpected results, a close inspection was made of the patient records and laboratory data and a positive correlation was found between the intensity of the reported side effects and poor anti-hCG antibody responses in some of the vaccine recipients. In all cases, these phenomena were associated with apparent or suspected instability of the emulsion vehicle. Because of the difficulty of developing, manually, the high shear forces needed to generate adequate emulsification, the vehicles of some of the vaccine doses formulated were probably unstable and separated into their oil and water phases soon after injection. Thus, instead of the

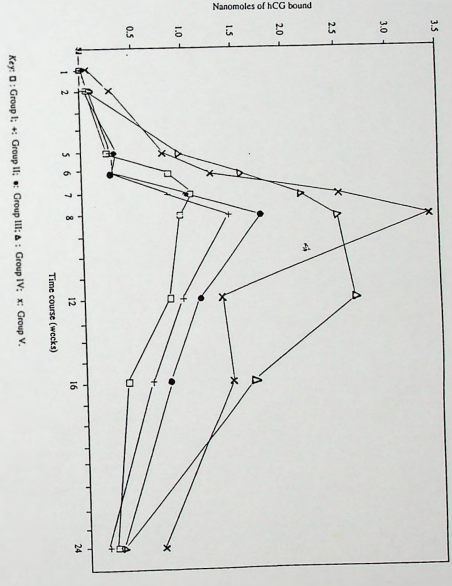

Fig. 1. Magnitude and duration of anti-hCG antibody titres raised in the five hCG vaccine dose groups in the Phase I clinical trial

MD, USA, has recently iniated a programme of research in this area under its Reproductive Immunology Initiative. The projects supported by this programme are concerned primarily with the identification and characterization of gamete antigens which might represent suitable candidates for FRV development.

- The National Institute of Immunology (NII) in New Delhi, India, has a large programme on FRV development and evaluation, ranging from the use of molecular genetics techniques to produce bioengineered vaccines directed at a variety of different reproductive targets, to the clinical evaluation of a number of different hCG vaccine formulations all of which use the whole ß-subunit of hCG as the primary immunogen (Talwar et al, 1986, 1987; Shaha et al, in press).

The Population Council in New York, NY,USA, is also supporting studies on the immunobiology of the gametes as well as a major programme of anti-hCG vaccine development in which the whole ß-subunit of hCG is used as the primary immunogen (Thau et al, 1985, 1987).

The USAID supported Contraceptive Development Programme (CONRAD) in Norfolk, VA, USA is primarily concerned with FRVs which will exert an effect prior to fertilization and is concentrating, therefore, on the identification and characterization of sperm antigens and antigens of the zona pellucida (Gupta et al, in press; Mahony et al, in press).

In addition to these major research programmes, there is a large number of investigators working independently in many countries in areas relevant to FRV development. Many of these activities have been stimulated by the recent expansion of knowledge of immune processes and developments in biotechnology and the increasing interest being shown by both academic and commercial institutions in the potential these developments offer for novel vaccine design and production.

The Task Force has defined research strategies and drawn up research plans in six principal areas. In addition to anti-sperm, anti-zona pellucida, anti-trophoblast and anti-hCG vaccines, studies have been proposed to reassess the feasibility of producing an effective local (secretory) immune response restricted to the lumen of the male or female reproductive tracts, and to carry out studies in the area of basic vaccinology relevant to the development of FRVs in general. Because of funding constraints, the Task Force's activities over the past biennium have been restricted to only two of these six areas of interest, namely the continuing development of anti-hCG vaccines and the initiation of preliminary studies aimed at the development of anti-trophoblast vaccines (Ada et al, 1986). However, some work has also been carried out, largely as a collaborative exercise with other agencies, on the establishment of a classification system for sperm membrane antigens.

Development of the anti-hCG vaccine

Virtually all vaccines in use and under development at the present time are directed against targets, such as bacteria and viruses, which express foreign antigens to which the vaccine recipient is not immunologically tolerant. Although hCG is a 'foreign' hormone, in the sense that it is produced in significant quantities only by the early embryo, the pregnant woman is tolerant to it and does not mount an immune response against it, either because hCG is very similar chemically to the endogenous pituitary hormone hLH or because of her prior exposure to hCG *in utero*. The development of an anti-hCG vaccine, therefore, is a totally new and experimental area of immunotherapy in which there is little previous information to guide investigators. To determine the feasibility of developing this novel approach to fertility regulation, two major questions concerning the efficacy and safety of the vaccine needed to be answered.

-- Could an anti-hCG vaccine break maternal tolerance to the hormone and elicit an immune response of sufficient magnitude to neutralize the hormone in the maternal circulation at the peri-implantation stage of 'gestation'?

-- Could the anti-hCG response so produced be restricted to the intended target so that cross-reactions with other normal body

constituents, particularly hLH, would not occur, and endocrine and metabolic disturbances and the potential risk of immunopathology avoided?

The mandate of the Task Force, therefore, was to develop a prototype anti-hCG vaccine to the point of initial clinical testing in order to obtain as much information as possible relevant to these two questions. Subject to a satisfactory outcome of the preclinical safety and efficacy work and the clinical study, further development would be justified to improve the vaccine to the point where it was suitable for use in family planning programmes. This final stage of development would be analagous to the structure/activity studies that are carried out with any new drug prototype in order to produce a preparation with maximum effectiveness and minimum side effects at the lowest possible dose.

The studies carried out under this section of Task Force activities address three principal objectives: the preliminary clinical evaluation of the safety and antifertility activity of the first generation anti-hCG vaccine; development of improved formulations of the current hCG vaccine preparation and the development of an optimized anti-hCG vaccine with improved components and characteristics; and the continued development of a baboon chorionic gonadotrophin (bCG) vaccine to permit the evaluation of the long-term safety and efficacy of this approach to fertility regulation in a relevant animal model system.

Phase I clinical evaluation of the first generation anti-hCG vaccine

The first generation anti-hCG vaccine developed by the Task Force, consists of a synthetic peptide representing the ß-hCG carboxyterminal 109-145 peptide (ß-hCG-CTP) coupled to a diphtheria toxoid (DT) carrier molecule, mixed with a muramyl dipeptide (MDP) adjuvant, and suspended in a squalene-arlacel-saline emulsion vehicle (Griffin, 1985, 1986; Stevens, 1986a-c). This complex preparation

Table 1. Composition of the vaccine and placebo preparations administered in the five dosage groups in the Phase I clinical study of the anti-hCG vaccine

Group number	Vaccine recipients	Placebo recipients	Immunogen (µg)	Adjuvant (µg)	Vehicle (µl)
I	4		50	25	25
		2		25	25
II	4		100	50	50
		2		50	50
III	4		200	100	100
		2		100	100
IV	4		500	250	250
		2		250	250
V	4		1000	500	500
		2		500	500

which it will be commercially available for use among the general populace.

Incidentally, the prototype vaccine -hCG-TT has also received an IND from the American FDA. Santiago, Santa Domingo and Helsinki will commence trials using this vaccine shortly under the aegis of International Committee for Contraception Research of the Population Council, New York.

The present trend is to use different carriers to afford protection against other diseases as well as to circumvent the problem of variability in immune response and mild hypersensitivity reactions seen in a few cases. The genetic makeup of individuals which may be responsible for some people responding to the vaccine better than others do, is also being investigated. Efforts are also being focused at developing polyvalent vaccines bearing more than one antigen of the reproductive tract. This will serve as a backup in case any one component of the vaccine did not succeed in blocking fertility by itself.

Problems

An anti-fertility vaccine unlike vaccines against infectious diseases, must be able to produce and sustain immunity in more than 95% of the vaccinated population. Human proteins are very difficult to produce in bulk amounts unlike most viral or bacterial antigens and are often non-immunogenic. Possible long-term effects on the foetus, if any, must also be studied before commencing mass immunization.

Contraceptive vaccines

Trials in India launched

New Delhi

CLINICAL trials of two locally developed birth control vaccines have started in India. Two hundred sterilized women volunteers recruited at five centres will receive the vaccines in a phase one trial to determine side effects, dose rates and relative efficiencies. The effectiveness of the vaccines in blocking pregnancy in unsterilized women will be assessed in a phase two trial, to begin by the end of the year.

The Indian Council of Medical Research, which has given top priority for immunological research in contraception, is supervising the trials of the vaccines, developed by a team led by Dr G. P. Talwar, director of the National Institute of Immunology in New Delhi. According to Talwar, the vaccines are improved formulations of the subunit hCG (human chorionic gonadotrophin) vaccine he developed twelve years ago, which went into clinical trials in five countries in 1976–78.

The vaccines prevent pregnancy by producing antibodies against hCG, a hormone secreted by the pre-implantation embryo which is essential for establishment and maintenance of pregnancy. Because the hormone is a 'self' protein, the trick is to make the hormone antigenic by tagging it to a suitable carrier. Talwar's early vaccine consisted of the purified and processed β-subunit of hCG coupled to tetanus toxoid (TT) carrier. The β-hCG–TT vaccine was tested in 63 sterilized women in India, Finland, Sweden, Chile and Brazil under a programme supported by the International Committee for Contraceptive Research in New York. It was found to be devoid of side effects, but further trials were abandoned because of poor antigenicity, wide variations in the amount of antibodies produced and low response in one-quarter of test subjects.

Talwar says these limitations have now been overcome, first by 'associating' the α-subunit of ovine luteinizing hormone (oLH) with hCG to raise its antigenicity and, second, by using two carriers, TT and cholera toxin-B (CHB), to take care of hyporesponders. The idea of using mixed carriers, according to Talwar, is that those who do not respond to one carrier will respond to the other.

What Talwar has now is a cocktail of antigens and carriers. Two vaccines have been standardized by the permutation and combination of these. One of the formulations under trial is a mixture of oLH–hCG–TT and oLH-hCG–CHB. The second formulation consists of a mixture of oLH–TT–CHB and hCG–TT–CHB. Both these formulations have been extensively tested on baboons.

Reporting the findings at a recent international conference on contraception in New Delhi, Talwar said his new vaccines produced twenty times more antibodies than were obtained with his first vaccine. He said the animals responding poorly to the single carrier responded extremely well to mixed carriers. In the absence of booster shots, the animals conceived and delivered normal babies, showing that the effect of the vaccine is reversible. With the launching of trials in India, there is now a race between Talwar and the US–Australian group that, last February, began testing a similar vaccine in Australia under the auspices of the World Health Organisation (see *Nature* 317, 288; 1985). That vaccine, developed by Vernon Stevens of Ohio State University, is based on the carboxy-terminal region of hCG conjugated to diphtheria toxoid.

The results of the Australian trial will be published first, but Talwar is sceptical of its outcome as he believes that carboxy-terminal β-hCG is only a poor immunogen. The carboxy-terminal peptide, however, is specific to hCG and, unlike hCG, does not cross-react with LH. According to Talwar, cross-reaction with LH is beneficial and not harmful. In fact, Talwar's first vaccine has now been cleared for human trials in the United States by the Food and Drug Administration.

Although Talwar was the first to put hCG vaccine into human trials in 1974, he lost the race because of controversies that cropped up after he jumped the gun. In a hurry to beat his competitors, he vaccinated six unsterilized women with hCG–TT vaccine in 1976 when its efficacy was still in doubt. Two of the women became pregnant, World Health Organisation withdrew support and questions of ethics raised by the Indian scientific community forced him to go back to the laboratory and animal trials.

Talwar says he now has more animal data to show his vaccines are efficient and safe. The babies born to the two immunized women are perfectly normal, a point stressed by Talwar to prove the vaccine's safety.

K.S. Jayaraman

A cautionary view of antifertility vaccines

SIR—K.J. Jayaraman's news report[1] of trials of antifertility vaccines comprising gonadotropin hormone subunits and their derivatives calls for some comment. First, it is not quite correct to state that one 'cocktail' of antigens and carriers used by G.P. Talwar for vaccination consists of oLH–hCG–TT (ovine luteinizing hormone–human chorionic gonadotropin–tetanus toxoid) and oLH–hCG coupled to cholera toxoid chain B (CHB), and a second mixture of oLH–TT–CHB and hCG–TT–CHB. In fact, the vaccines either contain the α-subunit of oLH (α-oLH) combined with the β-subunit of hCG (β-hCG) coupled to the two carriers, or β-oLH–TT–CHB and β-hCG–TT–CHB. A third vaccine, which was not mentioned, employs β-hCG–TT alone (for review see ref. 2).

More importantly, doubts arise concerning the hormone specificity, and therefore the safety, of the antifertility vaccines which either already are in phase I clinical trials or are planned to be by the Population Council and the Indian Institute of Immunology. Both groups claim that their carrier-coupled antigens are safe on the basis that α-oLH, β-hCG, β-oLH and α-oLH/β-hCG are either species-specific (because α-oLH and the α-chain of human glycoprotein hormones are considered immunologically distinct) or, if antibodies against hLH are elicited (because of similarities between β-hLH and β-hCG) they would cause no side effects. The first assumption is based on a concept of Vaitukaitis[3] which no longer holds true; only three monoclonal antibody-defined human α-chain epitopes support the assumption[4], whereas three other epitopes — one of which is only expressed by the non-assembled chain — are not only shared by all α-subunits of human glycoprotein hormones but are also present on α-oLH.

Concerning the immunological specificity of β-oLH and β-hCG chains compared with β-hLH, the situation is even worse. As Jayaraman states, there are numerous reports of immunological cross-reactivities (for example ref. 3). Monoclonal antibody based analyses reveal at least three epitopes shared between the two human β-chains[4,5], two of which are also common to oLH. Moreover, monoclonal antibodies against all these shared epitopes are able to inhibit the receptor binding ability of hCG as well as hLH. Additional side effects on the target cell from β-oLH/β-hCG vaccination might also be caused by antibodies which still have access to the receptor-bound hormone.

One possible way of circumventing the problem of shared epitopes would be to use for vaccination the hCG-specific carboxy-terminal peptide as done by V.C. Stevens and applied in the WHO supervised Australian trial[2,7]. If this turns out to be of poor antigenicity, as suggested by Talwar, it would be necessary to investigate further the truly hCG-specific epitopes[4] and try to isolate them or to construct appropriate mimotopes[6]. All other nonspecific vaccines have to be regarded with scepticism until their safety is clearly proven bearing in mind that they will eventually be applied to millions of people.

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39 of 162
TI: Gender comparisons of young physicians' perceptions of their medical education, professional life, and practice: a follow-up study of Jefferson Medical College graduates.
AU: Hojat-M; Gonnella-JS; Xu-G
AD: Center for Research in Medical Education and Health Care, Jefferson Medical College, Philadelphia, PA 19107-5083, USA.
SO: Acad-Med. 1995 Apr; 70(4): 305-12
LA: ENGLISH

40 of 162
TI: [Responsibility for patient education in trials of new procedures in humans from the physician's viewpoint]
AU: Schneider-V
AD: Institut fur Rechtsmedizin, Freie Universitat Berlin.
SO: Z-Arztl-Fortbild-Jena. 1994 Dec; 88(12): 1045-50; discussion 1050-4
LA: GERMAN; NON-ENGLISH

41 of 162
TI: [Consent and education in trials of new procedures involving humans--from the legal viewpoint]
AU: Deutsch-E
AD: Universitat Gottingen.
SO: Z-Arztl-Fortbild-Jena. 1994 Dec; 88(12): 1040-4
LA: GERMAN; NON-ENGLISH

42 of 162
TI: [Patient education regarding the suitability of medical practices, hospitals and alternative treatment methods--from the physician's viewpoint]
AU: Fritz-HG
SO: Z-Arztl-Fortbild-Jena. 1994 Dec; 88(12): 1031-4; discussion 1035-9
LA: GERMAN; NON-ENGLISH

43 of 162
TI: [Patient education regarding the suitability of medical practices, hospitals and alternative treatment methods--from the legal viewpoint]
AU: Jansen-C
SO: Z-Arztl-Fortbild-Jena. 1994 Dec; 88(12): 1027-31
LA: GERMAN; NON-ENGLISH

44 of 162
TI: A kidney donor's dilemma: the sibling who can donate--but doesn't.
AU: Bratton-LB; Griffin-LW
AD: School of Social Work, East Carolina University, Greenville, NC 27858-4353, USA.
SO: Soc-Work-Health-Care. 1994; 20(2): 75-96
LA: ENGLISH

45 of 162
TI: Physicians do not have a responsibility to provide futile or unreasonable care if a patient or family insists [see comments]
AU: Luce-JM
AD: Department of Medicine, University of California, San Francisco, USA.
SO: Crit-Care-Med. 1995 Apr; 23(4): 760-6
LA: ENGLISH

46 of 162
TI: Core and comprehensive health care services: 1. Introduction to the Canadian Medical Association's decision-making framework.
AU: Wilson-R; Rowan-MS; Henderson-J
AD: Department of Family Medicine, Queen's University, Kingston, Ont.
SO: Can-Med-Assoc-J. 1995 Apr 1; 152(7): 1063-6
LA: ENGLISH

47 of 162
TI: Clinical and ethical perspectives on rationing of high-cost drugs.
AU: Poirier-TI; Giannetti-VJ
AD: School of Pharmacy, Duquesne University, Pittsburgh, PA 15282.
SO: Ann-Pharmacother. 1995 Jan; 29(1): 78-81
LA: ENGLISH

48 of 162
TI: Implications of managed care for medical ethics. South Carolina Medical Association Medical Ethics Committee.
AU: Sade-RM; Marshall-MF; Roberts-JM; MacDonald-D
AD: Department of Surgery, Medical University of South Carolina, Charleston 29425.

SO: J-S-C-Med-Assoc. 1995 Feb; 91(2): 66-72
LA: ENGLISH

49 of 162

TI: [Ethics and cardiology]
AU: Vacheron-A
AD: Clinique cardiologique de l'hopital Necker, Paris.
SO: Arch-Mal-Coeur-Vaiss. 1994 Jun; 87(6): 783-9
LA: FRENCH; NON-ENGLISH

50 of 162

TI: Reflections in family practice. Family physicians as proceduralists: striking a balance.
AU: Brody-H; Alexander-GP
AD: Division of Primary Care, Agency for Health Care Policy and Research, Rockville, MD, USA.
SO: J-Am-Board-Fam-Pract. 1995 Jan-Feb; 8(1): 58-61
LA: ENGLISH

51 of 162

TI: Creating a dignified option: ethical considerations in the formulation of prehospital DNR protocol.
AU: Fitzgerald-DJ; Milzman-DP; Sulmasy-DP
AD: Department of Medicine, Georgetown University Medical Center, Washington, DC 20007.
SO: Am-J-Emerg-Med. 1995 Mar; 13(2): 223-8
LA: ENGLISH

52 of 162

TI: Public psychiatry's destruction of therapeutic trust. A negative lesson for general medicine.
AU: Lehrman-NS
AD: Kingsboro Psychiatric Center, Brooklyn, NY.
SO: J-Med-Assoc-Ga. 1995 Feb; 84(2): 65-9
LA: ENGLISH

53 of 162

TI: HIV-testing of health care workers: unethical request or moral obligation?
AU: Allerberger-F; Luthe-R
AD: Institute of Hygiene, University of Innsbruck.
SO: Wien-Klin-Wochenschr. 1995; 107(3): 91-4
LA: ENGLISH

54 of 162

TI: [Priority surveys: include the ethical principles in the health care law (interview by Jan Lind)]
AU: Einhorn-J
SO: Lakartidningen. 1995 Mar 8; 92(10): 933-6
LA: SWEDISH; NON-ENGLISH

55 of 162

TI: Issues of social policy and ethics in gene technology.
AU: Sade-RM
AD: Department of Surgery, Medical University of South Carolina, Charleston.
SO: Methods-Find-Exp-Clin-Pharmacol. 1994 Sep; 16(7): 477-89
LA: ENGLISH

56 of 162

TI: Essential vs discretionary health care in system reform [letter]
AU: Ashley-JT

SO: JAMA. 1995 Mar 22-29; 273(12): 918-9
LA: ENGLISH

57 of 162

TI: Core and comprehensive <u>health care</u> services.
SO: Can-Med-Assoc-J. 1995 Mar 1; 152(5): 740A-740D
LA: ENGLISH; FRENCH

58 of 162

TI: [An ethics for the future of the primary care team (editorial)]
AU: Altisent-R
SO: Aten-Primaria. 1995 Jan; 15(1): 1-2
LA: SPANISH; NON-ENGLISH

59 of 162

TI: [Indications]
AU: Frohmuller-H; Theiss-M
AD: Urologische Klinik und Poliklinik, Universitat Wurzburg.
SO: Urologe-A. 1995 Jan; 34(1): 62-8
LA: GERMAN; NON-ENGLISH

60 of 162

TI: Futility and the common cold. How requests for antibiotics can illuminate care at the end of life.
AU: Prendergast-TJ
AD: Division of Pulmonary and Critical Care Medicine, University of California, San Francisco.
SO: Chest. 1995 Mar; 107(3): 836-44
LA: ENGLISH

61 of 162

TI: Qigong therapy--its effectiveness and regulation.
AU: Tang-KC
AD: Southern Sydney Health Promotion Unit, Kogarah, New South Wales, Australia.
SO: Am-J-Chin-Med. 1994; 22(3-4): 235-42
LA: ENGLISH

62 of 162

TI: Long-term care, rehabilitation, and legal and ethical considerations in the management of neuromuscular disease with respiratory dysfunction.
AU: Hotes-LS; Johnson-JA; Sicilian-L
AD: Department of Medicine, Tufts University School of Medicine, Boston, Massachusetts.
SO: Clin-Chest-Med. 1994 Dec; 15(4): 783-95
LA: ENGLISH

63 of 162

TI: Ethics of rationing <u>health care</u> services [letter]
AU: Cox-D
SO: BMJ. 1995 Jan 28; 310(6974): 261-2
LA: ENGLISH

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TI: Reforming the Israeli health care market.
AD: [illegible] School of Public Health and Community,

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TI: [illegible]
AU: [illegible] Hammel-D; Roeder-N; Roetker-J
AD: [illegible] Thorax-, Herz- und Gefasschirurgie, Westfalische

64 of 162

TI: [Cost/benefit relations in heart transplantation]
AU: Scheld-HH; Deng-MC; Hammel-D; Roeder-N; Roetker-J
AD: Klinik und Poliklinik fur Thorax-, Herz- und Gefasschirurgie, Westfalische Wilhelms-Universitat, Munster.
SO: Z-Kardiol. 1994; 83 Suppl 6: 139-49
LA: GERMAN; NON-ENGLISH

65 of 162

TI: Reforming the Israeli health care market.
AU: Chinitz-DP
AD: Department of Medical Ecology, Braun School of Public Health and Community Medicine, Hebrew University-Hadassah, Jerusalem, Israel.
SO: Soc-Sci-Med. 1994 Nov; 39(10): 1447-57
LA: ENGLISH

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TI: Lifestyles and allocation of health care resources [letter]
AU: Goodman-NW
SO: J-Med-Ethics. 1994 Dec; 20(4): 271
LA: ENGLISH

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TI: In defence of ageism [letter]
AU: Rivlin-MM
SO: J-Med-Ethics. 1994 Dec; 20(4): 270-1
LA: ENGLISH

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TI: The Oxford Practice Skills Project: teaching ethics, law and communication skills to clinical medical students.
AU: Hope-T; Fulford-KW
AD: Oxford Practice Skills Project.
SO: J-Med-Ethics. 1994 Dec; 20(4): 229-34
LA: ENGLISH

69 of 162

TI: Are withholding and withdrawing therapy always morally equivalent? [see comments]
AU: Sulmasy-DP; Sugarman-J
AD: Division of General Internal Medicine, Georgetown University Medical Center, Washington, DC.
SO: J-Med-Ethics. 1994 Dec; 20(4): 218-22; discussion 223-4
LA: ENGLISH

70 of 162

TI: Homophobia and the moral authority of medicine.
AU: Wilkerson-A
AD: Department of Philosophy, University of Illinois at Chicago 60607-7115.
SO: J-Homosex. 1994; 27(3-4): 329-47
LA: ENGLISH

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TI: Tight budgets and doctors' duties [letter]
AU: Nicholson-CH
SO: Hastings-Cent-Rep. 1994 Nov-Dec; 24(6): 40; discussion 40-1
LA: ENGLISH

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TI: Tight budgets and doctors' duties [letter]
AU: Glasson-J; Orentlicher-D
SO: Hastings-Cent-Rep. 1994 Nov-Dec; 24(6): 40; discussion 40-1
LA: ENGLISH

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TI: Tight budgets and doctors' duties [letter]
AU: Baily-MA
SO: Hastings-Cent-Rep. 1994 Nov-Dec; 24(6): 40; discussion 40-1
LA: ENGLISH

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TI: The ethics of excess.
AU: Lamm-RD
AD: Center for Public Policy & Contemporary Issues, University of Denver, CO.
SO: Hastings-Cent-Rep. 1994 Nov-Dec; 24(6): 14
LA: ENGLISH

75 of 162

TI: Ethical and medico-legal problems concerning so-called hunger strikers.
AU: Neoral-L
AD: Department of Forensic Medicine and Medical Law, University of Olomouc, Czech Republic.
SO: Forensic-Sci-Int. 1994 Dec 16; 69(3): 327-8
LA: ENGLISH

76 of 162

TI: The inhumanity of fairness: rationing resources for reconstructive breast surgery.
AU: Wong-AM
SO: Can-Med-Assoc-J. 1995 Feb 15; 152(4): 577-9
LA: ENGLISH

77 of 162

TI: Caring for unhealthy lifestyles [letter]
AU: Alibhai-SM
SO: Can-Med-Assoc-J. 1995 Feb 15; 152(4): 469-70
LA: ENGLISH

78 of 162

TI: Ethical issues in physical medicine and rehabilitation. Conclusion to a series.
AU: Haas-JF
SO: Am-J-Phys-Med-Rehabil. 1995 Jan-Feb; 74(1 Suppl): S54-8
LA: ENGLISH

79 of 162

TI: Surgical issues in the management of carcinoma of the cervix in pregnancy.
AU: Lewandowski-GS; Vaccarello-L; Copeland-LJ
AD: Division of Gynecologic Oncology, Arthur G. James Cancer Hospital, Ohio State University, Columbus.
SO: Surg-Clin-North-Am. 1995 Feb; 75(1): 89-100
LA: ENGLISH

80 of 162
TI: [Increase the quality of Swedish hernia surgery! Improvement of long-term results is a challenge to occupational ethics]
AU: Nilsson-E
AD: Kirurgiska kliniken, Lasarettet, Motala.
SO: Lakartidningen. 1995 Feb 8; 92(6): 506-7
LA: SWEDISH; NON-ENGLISH

81 of 162
TI: Long-term effects of ethics education on the quality of care for patients who have do-not-resuscitate orders [see comments]
AU: Sulmasy-DP; Terry-PB; Faden-RR; Levine-DM
AD: Division of General Internal Medicine, Georgetown University Medical Center, Washington, DC 20007.
SO: J-Gen-Intern-Med. 1994 Nov; 9(11): 622-6
LA: ENGLISH

82 of 162
TI: Position of the American Dietetic Association: legal and ethical issues in feeding permanently unconscious patients.
SO: J-Am-Diet-Assoc. 1995 Feb; 95(2): 231-4
LA: ENGLISH

83 of 162
TI: HIV and AIDS. Legal and ethical issues in the emergency department.
AU: Derse-AR
AD: Center for the Study of Bioethics, Medical College of Wisconsin, Milwaukee.
SO: Emerg-Med-Clin-North-Am. 1995 Feb; 13(1): 213-23
LA: ENGLISH

84 of 162
TI: What do ethics have to do with lifestyle change?
AU: Starzomski-R
AD: School of Nursing, University of British Columbia, Vancouver.
SO: Can-J-Cardiol. 1995 Jan; 11 Suppl A: 4A-7A
LA: ENGLISH

85 of 162
TI: Removal of life support in intensive care units.
AU: Burrows-R
AD: Intensive Care Unit, Addington Hospital, Durban, South Africa.
SO: Med-Law. 1994; 13(5-6): 489-500
LA: ENGLISH

86 of 162
TI: Ethical challenges to the palliative care volunteer.
AU: Rothstein-JM
AD: Volunteer Services, Victoria Hospice Society, British Columbia, Canada.
SO: J-Palliat-Care. 1994 Autumn; 10(3): 79-82
LA: ENGLISH

87 of 162
TI: Ethics of palliative care in the context of limited resources: an essay on the need for attitudinal change.
AU: Dossetor-J; MacDonald-N
AD: Bioethics Centre, Edmonton, Alberta, Canada.
SO: J-Palliat-Care. 1994 Autumn; 10(3): 39-42
LA: ENGLISH

88 of 162
TI: Ethics of palliative care medicine: palliative care for the rich nations only!
AU: Olweny-CL
AD: St. Boniface Unit, Manitoba Cancer Treatment and Research Foundation, St. Boniface General Hospital, Winnipeg, Canada.
SO: J-Palliat-Care. 1994 Autumn; 10(3): 17-22
LA: ENGLISH

89 of 162
TI: Perspectives in genetic screening. Principles and implications.
AU: Kaback-MM
AD: University of California, San Diego.
SO: Int-J-Technol-Assess-Health-Care. 1994 Fall; 10(4): 592-603
LA: ENGLISH

90 of 162
TI: Genetic technology in health care. A global view.
AU: Galjaard-H
AD: Erasmus University.
SO: Int-J-Technol-Assess-Health-Care. 1994 Fall; 10(4): 527-45
LA: ENGLISH

91 of 162
TI: Changing the paradigm for informed consent [editorial]
AU: Dagi-TF
SO: J-Clin-Ethics. 1994 Fall; 5(3): 246-50
LA: ENGLISH

92 of 162
TI: Informed consent: pondering a new piece of the puzzle [editorial]
AU: Jacobson-JA
SO: J-Clin-Ethics. 1994 Fall; 5(3): 244-6
LA: ENGLISH

93 of 162
TI: Patients' perceptions of consent [editorial; comment]
AU: Shenk-I
SO: J-Clin-Ethics. 1994 Fall; 5(3): 243-4
LA: ENGLISH

94 of 162
TI: Patients' perceptions of the quality of informed consent for common medical procedures [see comments]
AU: Sulmasy-DP; Lehmann-LS; Levine-DM; Raden-RR
AD: Division of General Internal Medicine, Georgetown University Medical Center, Washington, DC.
SO: J-Clin-Ethics. 1994 Fall; 5(3): 189-94
LA: ENGLISH

95 of 162
TI: [High technology medicine in the year 2000.(Editorial)]
AU: Nel-CJ
SO: S-Afr-Med-J. 1994 Sep; 84(9): 587-90
LA: AFRIKAANS; NON-ENGLISH

96 of 162
TI: HIV testing and informed consent--ethical considerations.
AU: McLean-GR; Jenkins-T
AD: Department of Philosophy, University of the Witwatersrand, Johannesburg.

SO: S-Afr-Med-J. 1994 Oct; 84(10): 669-74
LA: ENGLISH

97 of 162

TI: The right to health care: an inevitable collision.
AU: Flecker-CA Jr
SO: Gen-Dent. 1994 May-Jun; 42(3): 256-7
LA: ENGLISH

98 of 162

TI: [Ethics and health care reform]
AU: Callahan-D
SO: Cas-Lek-Cesk. 1994 Dec 22; 133(24): 772-4
LA: CZECH; NON-ENGLISH

99 of 162

TI: AIDS and the emergency room physician and staff.
AU: Hirsh-HL
AD: Department of Health Care Administration, George Washington University, Washington, D.C.
SO: Leg-Med. 1994: 201-28
LA: ENGLISH

100 of 162

TI: Some moral problems in medicine [editorial]
AU: Warnock-M
SO: Health-Econ. 1994 Sep-Oct; 3(5): 297-300
LA: ENGLISH

101 of 162

TI: The role of ethics in quality and accountability initiatives.
AU: Veatch-RM
AD: Kennedy Institute of Ethics, Georgetown University, Washington, DC 20057.
SO: Med-Care. 1995 Jan; 33(1 Suppl): JS69-74; discussion JS74-6
LA: ENGLISH

102 of 162

TI: Profiling and performance measures. What are the ethical issues?
AU: Povar-G
AD: Department of Health Care Sciences and Medicine, George Washington University School of Medicine, Washington, DC.
SO: Med-Care. 1995 Jan; 33(1 Suppl): JS60-8
LA: ENGLISH

103 of 162

TI: Medicine's industrial revolution is here. Rally the Luddites [editorial]
AU: Hadler-NM
SO: J-Occup-Med. 1994 Sep; 36(9): 1038-40
LA: ENGLISH

104 of 162

TI: Marginal capacity: the dilemmas faced in assessment and declaration.
AU: Ho-V
AD: University of Toronto.
SO: Can-Med-Assoc-J. 1995 Jan 15; 152(2): 259-63
LA: ENGLISH

105 of 162

TI: Rationing health care: preparing for a new era.
AU: Wachter-RM

AD: Division of General Internal Medicine, San Francisco General Hospital Medical Center, CA.
SO: South-Med-J. 1995 Jan; 88(1): 25-32
LA: ENGLISH

106 of 162

TI: Ethical issues in managed care. Council on Ethical and Judicial Affairs, American Medical Association [see comments]
AD: Council on Ethical and Judicial Affairs, American Medical Association, Chicago, IL 60610.
SO: JAMA. 1995 Jan 25; 273(4): 330-5
LA: ENGLISH

107 of 162

TI: [Hemosurveillance: ethical and medicoeconomic constraints]
AU: Duprez-A
AD: CHU Hopital Central, Nancy.
SO: Can-Anesthesiol. 1994; 42(3): 411-4
LA: FRENCH; NON-ENGLISH

108 of 162

TI: The yin and yang of health care system reform. Professional and political strategies for setting limits.
AU: Daniels-N; Sabin-JE
AD: Department of Philosophy, Tufts University, Medford.
SO: Arch-Fam-Med. 1995 Jan; 4(1): 67-71
LA: ENGLISH

109 of 162

TI: Living wills and resuscitation preferences in an elderly population.
AU: Walker-RM; Schonwetter-RS; Kramer-DR; Robinson-BE
AD: Division of Medical Ethics and Humanities, University of South Florida College of Medicine, Tampa.
SO: Arch-Intern-Med. 1995 Jan 23; 155(2): 171-5
LA: ENGLISH

110 of 162

TI: Doctors and society--the Biko Lecture [editorial]
AU: Hoffenberg-R
SO: S-Afr-Med-J. 1994 May; 84(5): 245-9
LA: ENGLISH

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TI: Experimental treatment, values and rationing [editorial]
AU: Lie-RK
SO: Soc-Sci-Med. 1994 Oct; 39(8): 1011-4
LA: ENGLISH

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TI: Treating HIV infection: a question of ethics [letter]
AU: Pegram-PS
SO: N-C-Med-J. 1994 Nov; 55(11): 512
LA: ENGLISH

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TI: Treating HIV infection: a question of ethics [letter]
AU: Levine-RH
SO: N-C-Med-J. 1994 Nov; 55(11): 512
LA: ENGLISH

stings-Cent-Rep. 1994 Sep-Oct; 24(5): 36-8
LA: ENGLISH

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TI: The technological tether. An introduction to ethical and social issues in high-tech home care.
AU: Arras-JD
SO: Hastings-Cent-Rep. 1994 Sep-Oct; 24(5): S1-2
LA: ENGLISH

127 of 162
TI: Randomized prospective trial of estrogen-replacement therapy in women with a history of breast cancer.
AU: Vassilopoulou-Sellin-R; Theriault-RL
AD: Section of Endocrinology, University of Texas M.D. Anderson Cancer Center, Houston 77030.
SO: Monogr-Natl-Cancer-Inst. 1994(16): 153-9
LA: ENGLISH

128 of 162
TI: [Prioritization of fertilization in vitro--a systematic analysis]
AU: Ruyter-KW; Forde-R; Norheim-OF
AD: Senter for medisinsk etikk, Gaustadalleen 21, Oslo.
SO: Tidsskr-Nor-Laegeforen. 1994 Sep 30; 114(23): 2735-8
LA: NORWEGIAN; NON-ENGLISH

129 of 162
TI: United States and Canadian approaches to justice in health care: a comparative analysis of health care systems and values.
AU: Jecker-NS; Meslin-EM
AD: Department of Medical History and Ethics, University of Washington, Seattle 98195.
SO: Theor-Med. 1994 Jun; 15(2): 181-200
LA: ENGLISH

130 of 162
TI: How much ethics is needed to be a good doctor? [letter]
AU: Chowdhury-AW
SO: Lancet. 1994 Dec 24-31; 344(8939-8940): 1774
LA: ENGLISH

131 of 162
TI: In defence of ageism.
AU: Shaw-AB
AD: Bradford Royal Infirmary, West Yorkshire.
SO: J-Med-Ethics. 1994 Sep; 20(3): 188-91, 194
LA: ENGLISH

132 of 162
TI: Ethical dilemmas for general practitioners under the UK new contract.
AU: Smith-LF; Morrissy-JR
AD: University of Western Ontario, Canada.

SO: J-Med-Ethics. 1994 Sep; 20(3): 175-80
LA: ENGLISH

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TI: Bioethics in developing countries: ethics of scarcity and sacrifice.
AU: Olweny-C
AD: University of Manitoba, Canada.
SO: J-Med-Ethics. 1994 Sep; 20(3): 169-74
LA: ENGLISH

134 of 162

TI: Minimal breaches of confidentiality in health care research: a Canadian perspective.
AU: Emson-HE
AD: Royal University Hospital Saskatoon, Canada.
SO: J-Med-Ethics. 1994 Sep; 20(3): 165-8
LA: ENGLISH

135 of 162

TI: Equality, explicitness, severity, and rigidity: the Oregon plan evaluated from a Scandinavian perspective.
AU: Hansson-LF; Norheim-OF; Ruyter-KW
AD: Center for Medical Ethics, University of Oslo.
SO: J-Med-Philos. 1994 Aug; 19(4): 343-66
LA: ENGLISH

136 of 162

TI: Joseph J. Jacobs on alternative medicine and the National Institutes of Health [interview by Thomasine Kushner and Charles MacKay]
AU: Jacobs-JJ
SO: Camb-Q-Healthc-Ethics. 1994 Summer; 3(3): 442-8
LA: ENGLISH

137 of 162

TI: It is time to emerge from the trench and survey the whole battlefield.
AU: Lamm-RD
AD: Center for Public Policy and Contemporary Issues, University of Denver.
SO: Camb-Q-Healthc-Ethics. 1994 Summer; 3(3): 403-4
LA: ENGLISH

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TI: Outside the Garden of Eden: rural values and healthcare reform.
AU: Brown-KH
AD: Center for Health Policy and Ethics, Creighton University, Omaha, NE.
SO: Camb-Q-Healthc-Ethics. 1994 Summer; 3(3): 329-37
LA: ENGLISH

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TI: Ethical issues in physical medicine and rehabilitation. Conclusion to a series.
AU: Haas-JF
SO: Am-J-Phys-Med-Rehabil. 1994 Nov-Dec; 73(6): 436-40
LA: ENGLISH

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TI: The future of medicine [editorial; comment]
AU: Morrison-I; Smith-R
SO: BMJ. 1994 Oct 29; 309(6962): 1099-100
LA: ENGLISH

141 of 162

TI: Managed competition and managed care. What are the ethical issues?
AU: Jecker-NS
AD: Department of Medical History and Ethics, University of Washington, Seattle.
SO: Clin-Geriatr-Med. 1994 Aug; 10(3): 527-40
LA: ENGLISH

142 of 162

TI: Tube-feeding decisions in the elderly.
AU: Hodges-MO; Tolle-SW
AD: Department of Medical Education, Providence Medical Center, Portland, Oregon.
SO: Clin-Geriatr-Med. 1994 Aug; 10(3): 475-88
LA: ENGLISH

143 of 162

TI: Dialysis decisions and the elderly.
AU: Moss-AH
AD: Center for Health Ethics and Law, Robert C. Byrd Health Sciences Center of West Virginia University, Morgantown.
SO: Clin-Geriatr-Med. 1994 Aug; 10(3): 463-73
LA: ENGLISH

144 of 162

TI: The life and death of Miss Mildred. An elderly black woman.
AU: Dula-A
AD: Center for the Study of Ethnicity and Race in America (CSERA), University of Colorado at Boulder.
SO: Clin-Geriatr-Med. 1994 Aug; 10(3): 419-30
LA: ENGLISH

145 of 162

TI: Ethical issues and the breast cancer patient.
AU: Cummings-NB
AD: National Institute of Diabetes and Digestive and Kidney Disease, National Institutes of Health, Bethesda, Md 20892.
SO: Arch-Pathol-Lab-Med. 1994 Nov; 118(11): 1077-80
LA: ENGLISH

146 of 162

TI: Economic aspects of the care of patients in the vegetative state.
AU: Sailly-JC
AD: Universite Catholique, Lille.
SO: Acta-Neurol-Belg. 1994; 94(3): 155-65
LA: ENGLISH

147 of 162

TI: Discontinuation of total parenteral nutrition in a patient with acquired immunodeficiency syndrome: a Canadian perspective.
AU: Knowles-JB; Gilmore-N
AD: Nutrition Support Service, Deaconess Hospital, Evansville, IN.
SO: Nutr-Rev. 1994 Aug; 52(8 Pt 1): 271-4
LA: ENGLISH

148 of 162

TI: Health care as a right: some practical implications.
AU: Giesen-D
AD: Institute for Private Law, Free University of Berlin, Germany.
SO: Med-Law. 1994; 13(3-4): 285-96

LA: ENGLISH

149 of 162

TI: Medicolegal problems arising from AIDS and health care personnel with special reference to Spanish law.
AU: Gallego-Riestra-S; Martinez-Jarreta-B; Hinojal-Fonseca-R; Sanchez-Caro-J
AD: Catedra de Medicina Legal, Facultad de Medicina, Universidad de Oviedo, Asturias, Spain.
SO: Med-Law. 1994; 13(3-4): 241-9
LA: ENGLISH

150 of 162

TI: Ethical issues in genetic therapy.
AU: Penticuff-J
AD: University of Texas at Austin 78701-1499.
SO: J-Obstet-Gynecol-Neonatal-Nurs. 1994 Jul-Aug; 23(6): 498-501
LA: ENGLISH

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TI: Ethics in managed care.
AU: Fromer-LM
SO: Hosp-Pract-Off-Ed. 1994 Nov 15; 29(11): 51-2
LA: ENGLISH

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TI: The democracy problem [comment]
AU: Baily-MA
AD: George Washington University, Washington, DC.
SO: Hastings-Cent-Rep. 1994 Jul-Aug; 24(4): 39-42
LA: ENGLISH

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TI: To whom? [comment]
AU: Kamm-FM
AD: New York University, New York.
SO: Hastings-Cent-Rep. 1994 Jul-Aug; 24(4): 29-32
LA: ENGLISH

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TI: Four unsolved rationing problems. A challenge [see comments]
AU: Daniels-N
AD: Philosophy department at Tufts University, Medford, MA.
SO: Hastings-Cent-Rep. 1994 Jul-Aug; 24(4): 27-9
LA: ENGLISH

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TI: Responsibility and justice ... an ethical balance [comment]
AU: Reynolds-C
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WH 3.27

INTERVENTION IN HEALTH

(A People's Science Movement Programme)

A DRAFT FOR DISCUSSION

25 Questions

Q.1. What is the PSM planning in the health sector?

A.1 The PSMs are trying to evolve a programme that

a) improves the health conditions of the poor.

- the status of health of the poor in India is amongst the worst in the world. Almost all infant deaths and deaths at child birth are preventable. The resurgence of communicable diseases can be checked. And the quality of life can be increased considerably - now !

b) uses health as an arena for mobilisation of the weaker section

- The causes of ill-health lie in poverty and the poor working and living conditions of the people. A better understanding of health leads to this realization and therefore a health movement becomes part of a larger mass movement against exploitation and oppression.

c) uses intervention in health as an opportunity to empower people.

- People need more knowledge, skills and organisations to improve their quality of life and increase their say in local and national decision making. This is what we understand as empowerment. The nature of intervention in health is designed to promote such empowerment.

d) uses interventions in health to facilitate structures especially panchayats that would enhance people's power and sustain the gains.

- Health care must necessarily be planned for and implemented in a decentralized integrated, holistic fashion. Unless the panchayats are transformed, as well as simultaneously the nature of planning for and implementing health programmes changed a more effective public health policy will not emerge. Our programme must be designed to promote these objectives.

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c) will have an impact at a national or at least regional levels:

- One may have to start small. But unless the movement is eventually big enough it will fail to have an impact on policy making and it will be difficult to sustain. So our programme design must necessarily be replicable. It cannot be an understanding of NGOs delivering health by themselves or even as a parallel structure.

Q.2. What are the broad outcomes expected from the programme that one is designing the programme for ?

A.2.
a) a better utilisation of existing health facilities.
b) Better community awareness and participation in health programmes.
c) Better role for panchayats in ensuring accountability of health system.
d) Better mechanism for gathering health data and disease surveillance
e) Effective decentralized planning for health (with panchayats and health personnel in partnership)
f) Greater public awareness and emphasis by health system on preventive and promotive aspects of health care.
g) All the above must lead to measurable improvement in the health status of the population as well as a more active role for people in a transformed panchayat.

Q.3. What activities could lead to the above outcomes ?

A.3. The main activity areas identified are as follows

a) child health
b) women's health
c) waterborne diseases
d) other communicable and endemic diseases
e) disease surveys and disease surveillance
f) curative care.

In each of these these areas there can be three types of activities:

a) coordinated village level action - This will serve a mobilisational and educational purpose and ensure community participation. Certain specific intervention's can only be done by such group activity.

b) Individual person to person contacts: For meaningful impact on people's life and for the community to take the programme seriously, this is essential.

c) Administrative/Political action: Some steps for example provision of adequate drugs in the PHC, launching a food for work scheme in a particular area - can only be done by the state itself. Here the role of the programme is to act as a pressure group for this and ensure accountability of such functions.

Q.4. Specifically what can be done in child health in tune with the approach that has been outlined?

A.4. The suggestion is that every hamlet covered maintain a register that lists every child below 5. The list must be comprehensive taking special care not to miss out that 'last 5 per cent', that is the poorest and most marginalised sections. Then the immunization status of each child is entered and so too is the weight of every child, along with what level of malnutrition the weighing indicates. This process help us identify the malnourished child/classified as Gr.I, II and III. These people constitute the most vulnerable sections. The rest of the programme then becomes primarily the task of talking to the mother, assisting her to find ways and means to cope with child care given her limited time and money resources. Only well-trained health activists, provided excellent quality of support by the district or block team, can carry this out effectively. The health activist must have the skills to analyze and understand the mother and child's problem and suggest the solutions most appropriate to that specific context. In this process not only will they be able to ameliorate the malnutrition of the child but as part of doing this they will attend to completing immunization, deworm the child, give vitamin A supplements and appropriate timely management of diarrhoea and A.R.I. Indeed malnutrition cannot be managed without all these measures. Thus focussing on malnutrition becomes a focus on child health as a whole.

Q.6. But this is a difficult task ! Why not just focus on a single item - immunisation or diarrhoea control, etc - at least in the beginning.

A.6. Firstly all these problems of child health are closely inter-related and even if one wants one cannot handle one without the other. Immunization alone can perhaps be done but with a lot of effort and proportionately little impact on overall child mortality and morbidity. Secondly how can one sustain these interventions if done singly ? And finally if we are seriously talking to mothers it would neither be possible nor desirable to talk to mothers about ARI and about diarrhoea and not about malnutrition, etc. Perhaps immunization is the only single point intervention that can be done without talking to mothers about other aspects of child health and since it falls within the dominant perception of health as something delivered through injections and drugs it can still get accepted. For precisely this reason we would not take up immunization alone. Taking up child health with a focus on malnutrition has another advantage - it forces the programme to identify the most deprived and to interact with such families. An immunization campaign may be 90% successfull and still miss the most needy.

Q.7. But can our intervention make any impact on malnutrition ? After all this is mainly related to poverty about which this approach can do little.

A.7. Poverty's relationship to malnutrition is a bit more complex than simple cause and effect, or a simple failure of not enough money to buy food. A number of wrong or sub-optimal feeding practices, wrong perception of disease and health care and a wrong prioritization of time and resources contribute to malnutrition. A child from a more well off family may still get enough food and care despite wrong priorities but in a poor household every rupee counts and any assistance to more efficiently utilise scant resources is welcomed greatly by the mother. Still one cannot expect wonders. In a good one or two year programme we can hope to reduce grade III malnutrition significantly and to some extent prevent under 5 deaths. We are less likely to have an impact on Gr.I and II malnutrition. In such parameters one many need a generation of work for the impact to become measurable !

Q.8. But how does one make this a campaign? The work described looks more like a person to person to interaction done by health activists, rather than a mass campaign.

Q.8. In the total literacy campaign too, transaction of the primers was a person to person interaction. Yet we found enough occasions to generate the environment by well chosen campaigns. We must remember this relationship. Environment building and propaganda campaign without an individual follow-up makes the whole programme lack depth and seriousness (Imagine literacy jathes without any attempt to make people literate). On the other hand without environment building individual level action meets too much resistance and become impossible. In an area of child health too we can have balmelas or use camps to weigh children and immunization camps as environment building activities. The possibilities are limitless. The general principles are the same.

Q.9. What about women's health ? How do we propose to approach this area.

A.9. A wide variety of approaches are possible, depending both on the status of women and forms of discrimination prevalent in that area as well as the efficacy of existing health care delivery systems. In the worst states like in Bihar we are suggesting a major focus on raising the age of marriage. This may even be taken up as a broad-based social reform movement. At the village level one may consider forming village level committees to oversee this.; Other women's support activities like credit cooperatives (thrift groups) may be integrated with this. Even where age of marriage is not the central issue, the promotion of credit cooperatives, village libraries and counselling, support and information centres catering especially (if not exclusively to women) may form the central coordinated action.

If such activities form the coordinated village level action, the individual level action will largely relate to ensuring that all pregnant women received ante-natal care from trained

ANMs and have a trained dai to attend to delivery. Of course in those areas where no ANMs are available or willing to undertake this work the health activists may have to provide such care herself. (in which case she should be eventually absorbed as ANM).

The health activists will also need to be equipped to help women with primary health care for simple reproductive tract ailments and provide counseling for planning her family.

Q.10. What are our commitments to the family planning programme ?

A.10. We do not plan to undertake any campaign for family planning as such. We expect that our work in lowering infant mortality and in raising the age of marriage as well as providing support to women will in themselves prove to be an excellent promotion of the small family norm. Besides as part of provision of maternal care and reproductive health care we hope to equip the health activists to be in a position to provide a high quality of advice, especially for spacing. All this we expect to be reflected in better utilisation of MCH as well as family planning services in the sub centre and PHC level and may even, over time be reflected in lower fertility rates. However though we can study the impact on our work on such parameters, we will not have or accept any target whatsoever for family planning.

Q.11. The government of India and state governments have a major structure for just these purposes (child and women health). How does our programme relate to it ? How do the health activists of our programme relate to the health work of the government.

A.11. The health activist is the village or hamlet level assistance for the health worker who has far too many houses spread over far too wide an area to cover effectively. Therefore the health worker harassed and overworked as she is should welcome such assistance. And we must plan to build as strong links as possible between them.

The health activist is also the means by which the community learns about the work of the health worker and monitors it and builds up accountability of the health structure. To this extent the health activists (or for that matter this programme) may not be welcomed by health workers or local health authorities. This is one reason why it is necessary to keep health activists (or the earlier concept of village health guides etc.) under an independent body or district level NGO and not place it under the health authorities.

But there are certain functions of the health activists, as conceived, which are distinct from the health worker and have little overlap. The definition of the health activists as coordinating village level action (for example holding a balmela or organizing a credit cooperative) i.e., in mobilisation of people as well as in acting as the nucleus of a local pressure group for medical administrative or political action is one aspect that clearly demarcates and differentiates them from the health workers.

Finally one must note that while the government programme claims to cover women and child health, in practice it focus exclusively on family planning and immunization, with some attention to ante-natal care and training dais. In other areas like addressing child malnutrition, and other causes of child mortality as well as in addressing issues like age of marriage or reproductive health etc government programmes are often non-existent on the ground.

Q.12. What are the expected achievements in terms of the status of women's health ? Under what conditions can we hope to improve achievements ?

A.12. The bottom-line should be marked increase in the utilisation of all government provided services available at the sub-centre and PHC. Today, even where extensive infrastructure is created and there are adequate personnel, utilisation of services is extremely low. If the administration plans its actions jointly with our programme and implements needed steps on its side one can hope for a reduction increase in maternal mortality and morbidity. The spin offs from this campaign towards women's empowerment will be considerable if care is taken about the processes employed. Greater participation of women, erosion of negative cultural stereotypes creation of women's credit cooperatives, a higher age of marriage and stronger local women's organisation and movements can be expected outcomes from our intervention in women's health.

Q.13. What are the possibilities for intervention in water-borne disease which accounts for the greater part of all preventable diseases.

A.13. This is a question really of promoting sanitation at the personal, home and community level as well as the provision of safe drinking water. Existing sanitation programms are a dismal failure and even the provision of safe drinking water is far from achieved. A detailed understanding of these failures is essential but cannot be gone into here. One needs to construct an alternative approach. The basic principles of such an alternative approach are

a) The provision of safe drinking water must be a part of a comprehensive watershed management programme, using locally appropriate technology and involving the community in planning and in maintenance of such water sources.

b) Sanitation programmes must be comprehensive and planned for and implemented by the panchayat bodies assisted with adequate technical and financial resources and with the people's involvement.

c) Whereas community facilities (e.g., overhead tanks, common borewells, standpost, community latrines, etc) are built for at the state's expense, individual level facilities like domestic latrines, must be paid for by individuals. Subsidies must be very limited and if any is provided must be targeted only for the poorest and that too when the majority of the village have adopted the culture of using

toilets. On the other hand credit facilities, especially linked to credit cooperatives can be made available more liberally.

d) The provision of safe drinking water and sanitation facilities - not only latrines but all sanitation related products - soaps, tooth powder, smokeless chullahs, etc must become part of a huge employment generation programme and so structured that the employment and income so generated goes to weaker sections. Since both the generation of demand for these products and the considerable credit needed as well as the costs of community level structures all come from the government, it is important to ensure that the programme is so planned that the beneficiaries are not a few rich contractors but preferably cooperatives and groups of rural women and youth.

Some of these concepts have been tried out successfully in Midnapore district. They need to be replicated elsewhere but so far it has not been possible to generate the intra-organisational will needed for this. This concept known as the 'sanitary mart concept' involves its own environment building, production centre and a mechanism of sales of such products. (Further details can be had on request).

Q.14 What are the possibilities for control of other communicable disease (other than water-borne disease and immunisable diseases).

A.14 This is specific to each disease. Ideally a district authority or better still each PHC must draw up an estimate (based on surveys and analysis of outpatient data) of the numbers and nature of various diseases in that area. Then based on which diseases are causing the maximum loss o life of disability as well as a consideration of where there are possibilities of intervention, the diseases must be prioritised. Then working with the panchayats and NGOs a programme for their control must be evolved out. (Such an approach is an contrast to the present vertical programmes where priorities and methods are decided in the state or national capital).

To demonstrate the viability of such an approach it would be an excellent idea for our programme to take up control of one or two communicable diseases, in each district.

Q.15. Could we have any examples of a successful campaign against any infectious disease.

A.15. There are few. There is case of the programme against tuberculosis in Bangladesh. There is the Kheda malaria control programme and there are many examples of leprosy control.

Let us see the example of tuberculosis (as adapted for our needs).

A case detection camp for tuberculosis is held with adequate publicity and preparation. The camp is advertised as a camp for all respiratory diseases so as to improve attendance.

A doctor and a few MPWs can conduct it. The suspected cases of tuberculosis are subject to sputum examination then and there. Home to home visits and follow up ensure that no possible case is left out. The confirmed cases are all entered into a register. The necessity of ensuring that all of them take treatment for 9 months without break is not only explained to them but they are also required to sign or state a pledge to that effect before village elders. In some villages they were asked to give a money deposit also. (This deposit would be paid back once they completed the course). Then the health department (with some special mobilisation of resources) ensures that the local PHC has adequate stock of drugs and the health activists ensure its distribution. Such simultaneous identification and adequate treatment of all TB cases in an area is indeed the only sound approach to TB control. BCG has little value and just identifying a given number of cases per year and treating it will have no impact on stopping the spread of tuberculosis.

The control of leprosy uses a similar approach. Only the case detection camp for leprosy is conducted as a skin diseases camp. A considerable amount of pyoderma and impetigo and scabies and ring worm would therefore in the process get identified and treated too.

The control of malaria on the other hand requires a much more inter-disciplinary approach and much higher degree of organisation and community support and a much higher degree of state commitment. Results will take longer and need a greater input to sustain. But it is essential to reiterate that not only is a campaign against malaria possible, it would be ethically and practically impossible to ignore this problem in many places where malaria has a high endemicity.

Similar specific programmes against goiter, fluorosis or other health priorities can also be thought of.

Q.16. Why not take up a single disease like malaria for a national campaign. Would it not have a more visible and concrete impact ?

A.16. To fully understand why we do not recommend a campaign against a single disease one must fully understand our critique of the vertical health programmes and the causes behind the resurgence of infectious disease like malaria. *For more details contact us separately).* Our intervention must be adequate to reinforce the health delivery system as a whole in a given area and mobilize people and initiate local level planning for health. Necessarily therefore we must focus on local priorities and locally appropriate action plans instead of carry through a programme as part of a single point national plan. Besides for a disease like malaria in most districts the incidence will be less than 5 per 1000. That is a very high incidence but it does not create enough affected in a village to catch public attention readily. Only in those districts where the incidence is much higher or there is an epidemic outbreak will it become a public issue. It is therefore much more important in any participatory process, to identify the local priority, rather than declare one disease as priority centrally and then seek local community participation for it in each district, irrespective of how much that central priority is a local one.

Q.17. What can we do about disease surveillance and health intelligence ?

A.17. These are essential inputs for health planning and at present these mechanisms are virtually non-existent or non-functional. The government must more towards evolving viable district and block level health and disease surveillance mechanisms, that will be needed for local planning for health. We need to evolve and field test viable cost effective models for such disease surveillance (and health planning).

One viable example is the 'NATHI model' run by a department in CMC hospital Vellore with the Tamil Nadu government public health department. (This programme provides disease surveillance of ten diseases in the districts of North Arcot and Thiruvannamalai. This model has the advantage of involving a large number of private practitioners as well. It also provides regular inputs to health professionals on disease profile in the district and update them on therapeutic aspects of these disease. (For more details contact us *separately*).

Of course any such disease surveillance necessarily must be as a joint programme with the government. We hope to draw up a few such projects soon.

Within this present programme however we need to maintain a much better surveillance of child and maternal mortality. Unless this is done we cannot even ensure effectiveness of our own programme. This surveillance therefore is planned as a record of all births, deaths, pregnancies and marriages, maintained by the health activists with the assistance of health committee members. Guidelines have been evolved on the exact techniques of doing this and these too if not already with you are available on request.

Q.18. What about curative care ? Most people feel that unless we attend to curative care - their felt needs - no amount of emphasis on preventive care will be acceptable ?

A.18. This is a difficult question. We know for example that a number of CHWs have set themselves up as RMPs (a local term in use to denote a *'quack'* medical practitioner). Indeed it has been noted by some that when health workers function as curative practitioners, they have much better acceptance from the community. Do we accept or promote this trend in our health activists ? Some would say yes. Others would say no. A general consensus is that at least for two years they must be mobilizers, educators and preventive care practitioners rather than provide curative care. They can be trained in non-drug remedies and management of some common ailments especially pertaining to child and women health but they do not become barefoot doctors. If their lack of ability to give curative care is a handicap so be it. We will work actively for the community to see the health activist and thereby health as something more than curative care. The community learn to value and appreciate the visible impact made on child health and women's health especially by the health activist's interventions.

Simultaneously we can act as a pressure group to ensure adequate curative care at PHC and taluk/block levels. This will mean finding out whether doctors are attending regularly, whether adequate essential drugs are available, whether basic diagnostic facilities are functional and in preventing malpractice and irrational curative care. There is considerable scope in letting people known of the list of essential drugs that should be available and of the banned drugs and commonly used irrational drugs which waste their money.

A few groups have initiated work in promoting the growing of commonly used medicinal plants in kitchen gardens and training health workers to use them for some common ailments that are needed at the primary care level. Growing medicinal plants as an economically viable activity, processing them and selling them to local health care practitioners who use them have also be conceptualized though no such programme is on the ground anywhere to the best of our knowledge.

Q.19. What of the RMPs and ayurvedic and folk doctors and homeopathic doctors. Does the programme conceive involving them ?

A.19. First one has to recognize the fact, that it is these categories that in most places today provide the bulk of the primary -first level contact - curative care. The RMP is almost invariably someone who has worked as a doctor's assistant for a few months who has set himself or herself up. It may also be noted that when a qualified practioner is available many people prefer him or her as against an RMP but in most villages or even within 5 to 10 Km. no such doctor is available. Should we then involve the RMP ? Will they use it to legitimize their case ? Can we upgrade their skills ? These have to be worked out. But certainly one can involve them for surveillance of diseases as well as preventive care.

Much more thought and experience and study is needed on this question. However we should be more ready to involve 'well' qualified ayurvedic and homeopathic doctors.

Q.20. What about the qualified MBBS doctors? What role can the play in this programme ?

Firstly we must be worried that the prevailing cultures and structure of the medical professional does not promote their involvement in such programmes. Most will be apathetic and some may even be hostile. We should be ready for this. However properly approached a number of them may support this programme and contribute in the following ways:

a) May attend public functions, inaugurate workshops and can see patients in case-detection health camps.

b) Many may participate in disease surveillance efforts as most patients of certain types of disease will be seen by them.

c) May be of help in certain session of the training workshops- if given proper training material and training evaluation forms well in time. Please note that most doctors have no exposure to practical aspects of preventive health or even curative care at the level the health activist will encounter these problems. So without their using training material and being shown the evaluation forms it is not advisable to involve them.

d) May lead their names for the district level health committee. This is an important need.

It would be the invaluable if one or two doctors at least are PSM activists and in this capacity get involved in the district team. This will lead to a much better programme planning. The aim must be therefore to constantly educate friendly doctors on PSM perspectives and provide them with related information so that they develop their capabilities and are able to consciously rebel against the dominant negative trends in the medical profession trends which have played such a large role in creating an inadequate health care system and a retrogressive culture of health. At present many doctors who are in PSMs have developed this consciousness, and much of this was initiated by their being sensitized to these issues in rational drug prescription.

Even now it is essential to work amongst doctors on such issues as rational drug prescription, ethical issues in health care, medicial education methodologies so as to conscientize doctors to health policy concerns.

It may be pointed out that networks like AIDAN & NCCDP, and organisations like MFC and drug action forums, journals like Radical Journal of Health and Health Action and institutions like VHAI and FRCH, JNU social medicine department, to name a few have played a major role in initiating and developing this critique of health policies in India. What is being called a PSM understanding is not only the work of PSM organisations like KSSP, and DSF and PSF in health, but also of such other forces as named above. Such networks, organisations, institutions and journals continue to have relevance today and must be drawn upon to constantly provide intellectual inputs to develop our programme. Any one-upmanship in our approach to such groups will cost us dearly. What we need, is to, in parallel with this programmes, continue work with groups and on our own to develop our theoretical understanding of the crisis in medicine and in health care delivery, as well as a theoretical understanding of the alternatives.

Q.21. But if not doctors who can lead the programme - both at district and block levels.

A.21. At present most persons emerging in this role are social activists, who are working on health issues for developing an approach to social change. This commitment is crucial. In terms of backgrounds we would emphasize that at least half - if not more of the team at district and block level must be women. The main reason for this is that at the village level this is largely (like in literacy) a women's movement. In terms of qualification,

persons with paramedical training - health workers, nurses, health educators and supervisors, anganwadi workers etc are the best. They will also make the best quality of trainers (of course after some unlearning and some learning). Where the programme is being done as a project in collaboration with the government we should be able to identify two or three persons from this section (i.e., paramedics) who are already associated with people's science movements and get them on deputation for this role.

Two cautions however may be stressed. Firstly there must be no district or block level organizers or coordinator who is not capable of or involved in the process of training and providing support to health activists. Allowing a cadre of 'pure' organizers - persons with no knowledge of the specific technical aspects - is a serious danger for this programme.

Secondly whosever is providing such leadership must necessarily have some continuity and invest time and effort in developing capabilities - even if they are doctors - or health workers. There is a lot of learning involved and persons not capable of this need not be selected. (These warnings are made as sometimes some persons are selected on the basis of loyalty, obedience and an abstract understanding of 'being committed' or 'good organizers' !').

Q.22. Who are the health activists ? How is it planned to select and deploy them ? If voluntary for how long and after that what ?

A.22. Every hamlet or habitation should have one or two women as health activists. In case of large villages one would need about one per 200 households. More can be kept if funds to train and support them are available. Ideally the health activist should be a woman who is willing to spend part of her time on this work. If the person has enough literacy to comfortably read a booklet or take notes and fill a register that would be adequate. (This means about 5th class). Much more than this is not required. If a neoliterate committed to this programme is keen to play this role even this requirement can be waived. (We should specifically try to not keep women who are interested or likely to get jobs elsewhere).

At present there is no plan to pay any health activist. The work is fully voluntary. This voluntarism is possible only when her work is a part of a health movement that is people's movement for health. There must also be a very good quality of support. Without this mass movement approach and without regular support they can not continue on the task for long.

We expect the programme and health activists to continue for two years. After this what will become of them in an important question that we must think about.

This will depend on the impact of the programme itself and on the quality of the government structure. Where the government structure has been non-existent or weak

and unable to deliver, we can probably further upgrade the skills of the health activist to that of a health worker (ability to conduct delivery and basic curative care). Such a health worker must be paid by panchayats. The panchayats in their turn must be provided funds for these from the central and state health budget. But as this may take time to get, one can even consider panchayat raising funds for this. To prevent misuse by panchayats in this situation, a district level support body to monitor and support the health activists must continue (probably by a district level NGO). If on the other hand the government structure exists, its utilisation should improve and the health activists may have less to do in future except provide some voluntary support to them. Even in a situation where one has been unable to bring enough pressure to improve government structure and their utilisation, the health activist must be able to continue as part of a broad women's movement (or a rural youth movement).

Q.23. How is the training planned ?

A.23. We are proposing that first the district team is trained. It may take 8 days initially with two 3 or 4 day training after 6 month gaps. After the first eight days of training this district team trains health activists for 5 to 15 gram panchayats (about 20 to 50 health activists) and then conduct the programme in this 5 to 15 gram panchayats. The work in these panchayats is seriously re-viewed and they learn from it. They also complete a minimum reading in this area. This much can be done with little or no external funding. Then the programme can be expanded to 3 or 4 blocks (about 100 to 150 gram panchayats) and after this second year when enough resource person are available then perhaps to the whole district.

The health activists themselves are probably better trained in 3 or 4 day camps conducted once every 6 months, with a proper monthly review cum training meeting. Much of this learning will be through inservice training. Each spell of training will be on the immediate focus of the campaign. However where it is decided to upgrade them into health workers (preferably after 2 years) they should get a much longer at least 3 to 4 months training in a well equipped training centre where deliveries are conducted and basic curative care can be taught.

Q.24. What is the scale and duration of the programme ? What about funding ? In a given programme does one expect to take up all objectives set out or only some of them.

A.24. This has to be decided upon both availability of funds and our preparedness.
There are broadly four types of situations where we may find ourselves. First is a situation where there is no cooperation from either district or state authorities and no project. Even in such a situation one can do a lot. Indeed interventions in health may be one of the few intervention possibilities open to a PSM to keep their panchayat level units active. Of course in such a situation one should invest in building up a good district and block level team and then take up a few gram panchayats at a time and just one or two themes, for example women's health with child health or child health and malaria

and so on. Such activity can be critical in building up a capable health team and in strengthening our contacts.

A second situation is where there is no formal health project sanctioned, but one is able to find or raise some money from various funding sources. For example a common situation is that post-literacy programme funds can be used for this purpose by the simple expedient of choosing a suitable name like 'health literacy project' or 'strengthening PL through health literacy'' or 'functional literacy in health' etc. Again organisations like local charities, or some funds at a BDOs disposal or a body like Rotary etc can be tapped for some one activity at a time e.g. a training workshop or an anti-TB campaign, etc. About 6 districts in Tamil Nadu and 15 districts in the other states are today managing like this.

The third situation is when a formal proposal is submitted and approved. This is an optimum situation for it provides a full time structure that is essential to provide the health activists' with support. Besides it allows a much larger area to be covered and therefore a greater mass movement and impact. About 6 districts in the country today have submitted such proposals to the Ministry of Health and Family Welfare. If in these 6 districts the health department is also ready to innovate a plan for health at the district level an ideal situation becomes available for setting a new path in health care.

A fourth situation, which is true for most districts in the country is where the district PSM team itself is not ready. Here through a health education campaign, surveys and perhaps some gram panchayats level work a district team should be built up. Even if the government is willing to fund, we must not accept it. Invariably this would lead to implemeating a progrmame at conflict with our aims.

Q.25. But most of the causes of ill health lie in the economic policies of the government - and the structural adjustment advocated by the World Bank. Does not taking funds from the government compromise the opposition to these policies. Indeed the World Bank wants the government to give attention to some aspects of health care (e.g., infant mortality) as part of its safety net concept. The central role of the PSM must remain bringing pressure to bear on the state for changing its policy and in the process exposing the true nature of the state (and the roots of ill health). Providing services, even as a measure of relief for the people cannot be done, without diverting away from our central task. This is all the more true if one accepts government money. And to say that we will do it voluntarily or build systems where people, especially the poor pay for their health is very much the World Bank line.

A.25. The question raises a mix of very different issues but as this is the way in which many articulate this let us try to sort it out.

Yes. The economic policies of the government, which are World Bank inspired have a major role to play in creating ill-health. And yes mobilizing people against these policies

is a central task. No, we are not saying that people will pay for their own health nor are we building any parallel health systems. The proposed programme reinforces and places a demand for strengthening existing health infrastructure and government expenditure. And no, what the World Bank says or does not say is not an adequate factor to decide our course of action. Precisely because health is a vital area where its policies become exposed, the World Bank seeks both legitimacy and safety in organizing interventions in health. This cannot make us ignore this area. Our aim should be to choose a process most suited for mobilisation of people.

What can be the tactics of mobilisation against the present state's policies, especially as pertaining to health ? Yes. Holding seminars and meetings and publishing books and articles in the press can be ways of building pressure for policy changes. Such forms of mobilisation will be very effective not only for winning support amongst the liberal intellectual and academicians but also in the larger politically important middle classes. Today when vast sections of this class are swayed by the apparent success of economic reforms (perceived in terms of both growth rates in press reports and in the increased availability of consumer goods and certain types of jobs) one needs to bring home the human cost of the Structural Adjustment Programme by highlighting their impact on health.

But we hold that for mobilizing the vast sections of those who are most affected by these reforms and policies, such a tactics of pressure or protest may be inadequate. If we must use their ill health as the focus of mobilisation we cannot do it without organizing to assist them in coping with ill health. This is in contrast to merely 'demanding' that the state be held responsible. Ask any trade unionist. He knows that without helping the worker defend their wage levels and without help on a number of shop-floor issues - organizing workers for political change is quite impossible. The fact that such interim gain are in trade union struggle conceded by the owner or state and such interim gains in a health movement are secured by people's voluntary contribution is of course there and this does make a difference. But it is highlighted here to counter arguments that pose winning interim gains or concessions for the people as inherently 'reformist' or diversionary.

Another major reason for a 'constructive campaign' as opposed to a more oppositional or protest campaign is that the impact of the economic reforms on health is not perceived as such. Diseases are perceived largely as individual events affecting each individual due into natural factors. It is difficult to read politics into an epidemic of diarrhoea or even an infant death.

Why, surprisingly a large numbers of mothers of malnourished children do not even perceive these children as malnourished. (often doctors too can identify only grade III malnutrition). Time and again we have talked to such mothers to find them insisting - "No, its not food my child needs. Its tonic and medicines'. In such a culture of health, and given the structure of the health delivery system the route of organizing the suffering

poor for protest as usually understood, can even be counterproductive. For very often demands that are not genuine needs, but wants created by the culture of health, get voiced. We must learn to recognize that modern day capitalism does not depend solely on state power to defend its pro-rich economic policies. It is able to alter the nature of the production and distribution and knowledge as well as to generate a culture that manufactures consent for its policies. This is clearly evident in health where social problems are perceived as medical ones and people perceive health as a matter of pill-popping - of controlling diseases by consuming the doctors services, drugs and diagnostics. The state as government, often dissociates itself from this culture and even makes ineffectual protest against it, leaving it to its worthy allies in the medical profession and the health industry to defend and promote this culture. To the profession and to the industry the existence of this culture is an occasion for super profits, not a cause for dismay.

Whereas the politics of protest focuses all its attention on the state if fails to grasp the modern reality that power is not concentrated in the state but lies diffused through the institutions of civil society, and is effected as much by culture as by force.

If the terrain of conflict is culture and the nature of knowledge and the way people perceive and value health, then it makes far more sense to choose a form of mobilisation where such issues are focussed on. In such a perception of conflict, the health activist talking to the mother of a malnourished child or a village organizing a sanitation campaign is no longer incidental to the change process or purely tactical - it becomes centre stage. Similarly if the terrain of conflict is seen as questioning the structure of health care delivery and working to radically restructure it then an activity like drawing up a district or panchayat level health plan, or involving panchayats in health care, becomes effective tools of mobilisation of the poor.

By reducing these issues to the issue of funding or no funding the emphasis gets shifted off the real issues. One can see a number of non-funded programmes that reinforce the dominant culture of health and reinforce its negative structural features. Indeed precisely because they are easier to do without funding such activities get priority. Thus very often we see groups running health camps or centre where free medical check up and drug distribution is provided - often as their sole activity. Or we hear demands being raised for more government expenditures in certain areas where the existing approach and the structure of delivery used lead only to a larger leakage or serve as political patronage. Demands for increased government expenditure are usually in an absolute sense justifiable but without restructuring delivery mechanisms they are counter productive. But these same forces may never make the demands for restructuring the health care delivery system a part of the demand for increased expenditure.

Paradoxically when finally government funding is conceeded within our organisation it is done not with any understanding of the nature of conflict and therefore the nature of mobilisation needed, but merely as an adhoc approach e.g., one needs it to sustain

organisation etc. The result of this is that the door becomes open to seek funding from all sorts of government schemes most of which serve to reinforce existing health structures and existing culture. It is obvious that funding will become available for a target oriented family planning programme easier because it fits in with the existing wisdom on family planning and the existing structure of health care delivery. (This is much more true in developmental areas like watershed management (done without concern for equity) or employment generation by encouragement of piece rate putting-out systems - e.g., gem cutting, shampoo packing or IRDP type loans for cows, etc.

It is the way we do health, the processes we use (and refuse to use) that are critical to determine whether real mobilisation and empowerment results and radical change is being approached or not. One can achieve success both in terms of organisational influence and even in a limited sense in terms of health statistics without any empowerment by using existing cultural idioms and encouraging structures favourable to the dominant paradigm. But the organisations so created may even become an impediment to change. The emphasis must therefore be on designing and implementing programmes to fulfil our objectives.

One other corollary of this discussion needs to be stressed. If the terrain of conflict is the culture of health and the structures of health care delivery' then the leadership of this campaign needs to be equipped to lead in these areas. Organizers who are not so equipped, are likely to take on uncritically the prevailing scientific and technological view points as neutral knowledge and lead the programme astray.

This draft is prepared and circulated by me on the basis of discussion and experiences so far within the AIPSN/BGVS sub committee on health.

On many of these issues there may not be a clear consensus but unless we put down in paper our views and identify how exactly we differ, no clear consensus will emerge. This note is therefore circulated for initiating such a wider discussion. If all state and where existent sub committees on health as well as state PSM executive committee, could respond to this note (in writing) by suggesting further questions or modifications in the given answers, which would help us plan for a more meaningful discussion at the AIPSN congress at Bhopal.

Dr. T. Sundararaman
for Sub committee coordination on health

partner tracing

People with sexually transmitted diseases are urged to divulge partners' names, and the new medical detectives track them down. LORI MILLER KASE reports

Cathy Raevsky, an intelligent, compassionate thirty-three-year-old, walks up to a stranger's doorstep, silently rehearsing the devastating message she is about to deliver. Paying visits like this is the most difficult part of her job.

The woman who answers the door—a well-dressed blond, about twenty-eight years old—fits the description perfectly. "Can I speak to you privately?," Raevsky begins. "I am from the state health department, and I have important information concerning your health." Not until the woman steps outside and shuts the door does Raevsky continue.

"The reason I'm here is because you have been exposed to the virus that causes AIDS," Raevsky says in the calming tone she has perfected over the years.

The question is: are people willing to kiss and tell?

"One of your sexual partners has tested positive for HIV." The woman, who has had only one sexual partner—her husband—for the past eight years, is stunned.

Raevsky, associate director of the Colorado Department of Health's STD/AIDS section, has been notifying the sexual partners of HIV-positive patients for the past three years—and STD-infected patients for more than a decade. "It never gets easier," she concedes. "You just get better at dealing with people's reactions. You try to make them understand that exposure to HIV isn't necessarily a death sentence. It's hard because you're never the good guy, you're always delivering bad news."

Raevsky's message deals a crushing blow. Often the person she contacts must confront the reality that her partner (and perhaps she, too) carries a potentially fatal disease. The underlying message can be just as devastating: the partner may have been unfaithful. And in many cases, not with another woman, but with a man.

What happened to the young woman Raevsky visited? No one knows. Once partners are urged to get testing and counseling, and encouraged to divulge the names of sexual and IV-needle-sharing contacts, the files are essentially closed.

The new medical detectives—people like Raevsky who track down the unsuspecting partners of AIDS patients—are messengers with a mission: they believe potentially infected people have the right to know they're at risk. They hope to reach people *before* they become infected, giving them the chance to protect themselves. The reality, though, is that many of the people they contact already carry the deadly virus—and must be alerted before they spread the disease.

Raevsky, along with twenty-three colleagues at the Colorado Health Department, tracks down an average of nine hundred people each month: some are the partners of people who have tested positive for the human immuno-deficiency virus (HIV); others are the partners of people with other sexually transmitted diseases (STDs) like syphilis and gonorrhea. Though Colorado is ranked nineteenth in the country in number of AIDS cases and falls well below the nation's incidence of other STDs, the state has one of the most active "contact-tracing" programs around.

Colorado's medical sleuths come from a variety of backgrounds, but all are specially trained in contacting and counseling potential AIDS/STD victims. As Raevsky puts it: "You don't just say 'Hi, I'm from the health department. Who are you sleeping with?' " Field investigators must survive a rigorous screening process—only about 20 percent of applicants do; then they spend about five months attending classes, role-playing, and tagging along with senior investigators. For novice investigators, the first few months are emotional minefields. Says Raevsky: "You're worried you're going to cause someone psychological harm."

How do people react to Raevsky's visits? Reactions vary, she says, from tears or angry outbursts to simple surrender. "Who gave you my name?" is a question commonly asked, but never answered. "If we blow confidentiality," says Regina Olson, a former health department clerk-typist who has been investigating AIDS/STD cases for the past two years, "we lose the trust of the people we talk to."

People who test positive for HIV are given the option of informing partners themselves. But according to Olson, though 97 percent of those interviewed at an STD clinic said people should be informed when they come into contact with someone with AIDS or another STD, most admitted they would find it difficult to tell their partners themselves if they were infected.

States have been notifying the partners of people with STDs other than AIDS—especially syphilis and gonorrhea—for decades. In the past few ▶ 262A

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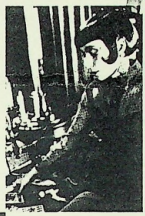

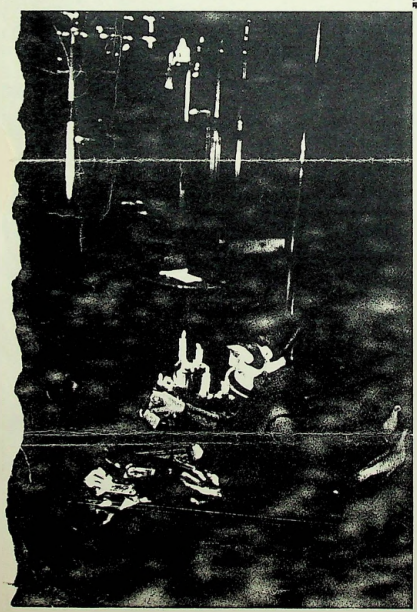

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Notes on talk delivered at CHAI-KA AGBM on 16/09/96 as panelist on 'Health as a Human Right'.

Topic : **Role of Voluntary Agencies**

- 1. It is difficult to delienate the role of Voluntary Agencies in Health, primarily since we have started our work as organisations or individauls with a set of Aims and Objectives unique to our perspective.

  We are also caught up in our work towards this, focussing on the Annual reports, Evaluations and such other imperatives leading to our Goals/Aims/Objectives. it is only at such meetings or seminars that we look at wider/deeper/emerging issues and attempt to put it into our working framework.

- 2. Our work revolves around the services we provide, lobbying and networking we do, attempting as Holistic an approach as possible within our framework. We do address the Physical, Mental, Social and Spiritual dimensions of Health within our limitations. This is usually, the addressing of Disease among the people we work with.

- 3. Does this address the needs of Health as a Human Right? I will be deliberately not addressing the issues of Poverty and Gender discrimination already elaborated on by the other panelists. That they are issues of prime importance is without doubt. The great social reformer Swami Vivekananda had said that it is criminal to talk of religion to people having empty stomachs. It is the same with health too!

- 4. The changing scenario in which Voluntary agencies operate needs an understanding. We are in the midst of a number of revolutions occuring simultaneously, and adjusting our focus to Health as a human-right amidst all these is important. They are,

  - a) The Communication revolution, making our planet a truly global village. The world is aware of anything going on at even remote places. How does this help Health & Human rights?

  - b) The Gender revolution - seen even in remote villages, where women are becoming active participants in life around, though may not be at the pace/in areas desired. A change is definitely happening.

  - c) The Economic revolution, where we see that the rich are becoming richer, and the poor, poorer - despite hopes and proclamations to the contrary.

And,

-d) The Spiritual Revolution, manifesting as religious fundamentalism and terrorism at one end, and small spiritual-seeking groups working for peace and harmony at the other.

- 5. In this scenario, what we need to think about constantly is, - Are we working towards our own goals, or towards those of the people we are working with? The needs, priorities and satisfaction is of the people - not ours.

We are caught in a paradox because of this - we need to have the **EMPATHY** as well as maintain an **OBJECTIVITY** to be successful in our work with the people.

This type of work demands from us, multiple roles and multiple capabilities. It can only be obtained with team-work and networking. Are we geared to do all this?

-6. Another major requirement of the Voluntary agency role is the ability to **COUNSEL**. It is an onerous task indeed, demanding not only skills, but also the information base and the ability to demystify and transmit/communicate this to suit the needs of the people.

To summarise, we need to truly understand, that the corollary of **'Rights'** is **'Responsibilities'**. As voluntary agencies, we have stepped forward to take these responsibilities and need to work towards our own level, till the time people take this 'responsibility' onto themselves along with the rights.

It means that we go beyond identifying human-rights violations and rectifying them, to a positive approach of building up the concepts of human-rights in all work that we do.

Thank You.

DR. SHIRDI PRASAD TEKUR.

sterilization will remain a highly important contraceptive choice in spite of developments of other effective spacing methods.

CONTRACEPTIVES OF TODAY AND TOMORROW

The need for evolving more acceptable and effective means of contraception with nil or minimum side-effects is more acutely felt than ever before in view of the frightening rate at which the population is growing. The world population has already crossed the five billion mark out of which about 800 million live in India at present. Time is precious and this field is emerging as one of prime importance in biomedical research and is attracting scientists and investigators from a variety of disciplines - biology, medicine, chemistry, biochemistry, immunology, biophysics and biomedical engineering, to mention a few. This veritable fusion of disciplines in a way reflects the range of problems encountered in deciphering the laws of living systems. In the last two decades, a great deal more effort and work has gone into surveillance of the pill, IUDs, abortion techniques and sterilization than was devoted to the initial development of these forms of contraception. We now know more of the dangers and benefits of the oral contraceptives which have been greatly improved and made safer by lowered dosage levels. The second generation of IUDs perform somewhat better than the first but no really fundamental breakthrough has occurred. Sterilization cases have increased much more than was envisaged in the 1960s and there have been important simplifications in its application in women. Surgical abortion techniques have proved far safer than anticipated when the medical termination of pregnancy was liberalized in India. However, there is no male pill on the market and no safe and simple menses inducer (postovulatory contraceptives).

The recently developed methods of contraception include hormonal contraceptives and medicated IUDs. While the oral pill has undergone drastic modifications in terms of the doses of the steroids used, other drug delivery systems have been developed for delivery of these steroids at a low dose for long-term protection. The medicated IUDs include the Copper T and progestasert (Progesterone-containing IUD).

Long-acting Steroids

Long-acting progestogens were synthesized during the 1950s and occasionally used in the treatment of gynaecological diseases. A variety of progestogens and combination of progestogens and estrogens have now been used as injectable preparations or as subdermal implants. The Chinese have developed a once-a-month pill. Before the year 2000, women around the world may have a number of long-acting contraceptive methods to choose from. All these methods are developed with long-acting steroids. They are safe, effective, convenient to use and do not require the taking of a pill every day. However, cycle control may be a problem.

Injectables

Two long-acting injectables are widely available-depot medroxyprogesterone acetate (DMPA; trade name Depo-Provera; the Upjohn Company, USA) and norethindrone enanthate (NET-EN; trade name Noristerat; Schering AG, West Germany). Both are highly effective spacing (reversible) methods. DMPA is approved for use in more than 90 countries; and NET-EN, in more than 40 (but not in India).

DMPA was synthesized in 1954 and the depo preparation was first tested as a contraceptive by Tyler and Coutinho and De Souza (1966). In the world as a whole, about one and a half million women are using DMPA as a contraceptive and over 10 million women have used it at some time or other. It is normally given as a three-monthly intramuscular injection of 150 mg although regimens extending to six months or more have been used. Within 24 hours of injection, serum levels reach 2.6 - 7.8 n mol/L and plateau at 2.6 - 3.9 n mol/L over the next two to three months (Ortiz *et al.* 1977). Once released from the depo site, DMPA is cleared from the blood stream within about 24 hours. In a randomized trial of two DMPA doses, none of the women receiving the standard 150 mg dose conceived, but the pregnancy rate among women receiving 100 mg every three months was 0.44 per HWY (WHO, 1986). With higher doses and a longer injection interval -250 to 450 mg every six months - pregnancy rates have ranged from 0 to 3.6 per HWY (McDaniel and Pardthaisong, 1974; Rall *et al.* 1977).

Other long-acting injectables include chlormadinone acetate, 17-hydroxyprogesterone acetate, lynestranol phenyl propionate and norethisterone enanathate (NET-EN). Only the latter has achieved widespread use, but on a still more limited scale than DMPA. NET-EN is given in both 2 months and 12 weeks regimens. With the 12 weeks regimen, the first three 200 mg injections are given at 8-weeks intervals, and subsequent injections are given at 12-weeks intervals. The 2-month regimen is markedly more effective. Two-year cumulative life-table pregnancy rates with the two-month regimen range from 0.4 to 1.8 per 100 women (ICMR, 1984). In contrast, with the 12 weeks regimen, 2-year rates are as high as 6.6 per 100 women (WHO, 1983). However, maximum protection against pregnancy is observed when the injectables are administered during the first week of the cycle. Any delay may not prevent ovulation in that cycle and thereby the risk of pregnany is increased.

The long-acting injectables abolish the cyclical release of LH and FSH, probably by an action at the hypothalamic level as observed with combination of oral pills. However, injectable contraceptives seem to have less effect on overall bodily physiology, *e.g.* liver or thyroid function, than do the oral pills but they have a more profound effect on the genital tract.

TABLE 5

CHARACTERISTICS AND STATUS OF LONG-ACTING INJECTABLES AS ON MARCH, 1987*

Hormone	Development and Testing	Duration of Action	Status of Animal Trials Phase I	Status of Human Trials Phase II	Phase III	Availability
DMPA (150 mg Depot Medroxyprogesterone acetate)	Upjohn Co.	3 months	Completed	Completed	Completed	Approved in over 90 countries
NET-EN (200 MG Norethindrone enanthate)	Schering AG	2 months or 12 weeks	Completed	Completed	Completed	Approved in over 40 countries
HRP 002 (6.25, 12.5 & 25 mg. Levonorgestrel butanoate)	WHO HRP	3 months	Underway	Completed in 3 sites in 50 women	To begin in mid 1987	Expected to be available in 1992
HRP 011 (20.40 & 60 mg. Levonorgestrel 3-oxime cyclopentyl carboxylate)	WHO HRP	2 months	Completed	Underway in 3 sites in 30 women	To begin in early 1988	Mid 1990s

WHO HRP = World Health Organization, Human Reproduction Programme

*From Population Reports, Series K, No 3, March-April, 1987.

There are no serious adverse reactions encountered in those receiving injectable contraceptives. The major side-effect is on patterns of menstruation - irregularity to amenorrhoea. The overall blood loss is reduced but occasionally there are episodes of heavy bleeding (Koetsawang, 1980). Many women gain weight on DMPA or NET-EN, often as much as 0.5 - 2 kg. in the first year.

Numerous studies have shown that the use of injectable steroids is associated with a slow return of fertility. The median time to conception is about 10 months after the last injection with fertility returning to 75 per ent of women within 15 months and to 95 per cent in 24 months (Pardthaisong *et al.* 1980).

Neither DMPA nor NET-EN has any adverse effect on the amount and duration of lactation and infants of DMPA and NET-EN treated mothers gained weight more rapidly than controls.

The greatest debate concerning the use of long-acting steroids has revolved around possible carcinogenicity. In some studies, a higher prevalence of abnormal cervical smears has been recorded in DMPA users (Litt, 1975) but not in others (Dabancens *et al.* 1974). The prevalence rate declines with duration of use and there is no evidence of any change in the risk of invasive cervical cancer. Another area of concern is the possible relationship between continuous low levels of progestogens and the incidence of breast cancer. So far only two cases of breast cancer among DMPA users have been reported (Zanartu *et al.* 1983) but this is not unlikely in the case of a common disease. Liang *et al.* (1988) followed up 5000 women for 4-17 years after their initial DMPA injection and found that relative risk of breast cancer was 0.7 (95 per cent confidence limits 0.3 - 1.4).

TABLE 6

RISKS OF VARIOUS CANCERS AND DMPA USE, WORLD HEALTH ORGANIZATION - 3 COUNTRY CASE-CONTROL STUDY 1986

Site of Cancer	No. of cases who used DMPA/ All cases (%)	No. of controls who used DMPA/ All Controls (%)	Relative Risk for women who have ever used DMPA*
Breast	39/427(9)	557/5951(9)	1.0
Cervix	129/920(14)	545/5833(9)	1.2
Ovary	7/105(7)	74/637(12)	0.7
Endometrium	1/52(2)	30/316(9)	0.3
Liver	7/57(12)	34/290(12)	1.0

*Adjusted for centre and for factors known to affect cancer risk. None of these relative risks is significantly different from 1.0. WHO (1986)

Since 1980, regulatory agencies in Sweden, the UK, France and West Germany have approved DMPA for contraception. Several national and international scientific groups have also endorsed DMPA, including WHO, HRP and IPPF.

Monthly Injectables: Monthly injectables are widely used in Latin America and China. The monthly injectables contain an oestrogen and a progestin combined. These are highly effective. WHO is currently supporting research on two new monthly injectables which appear to be effective and safe and may be available by 1988.

Oestrogen-progestin combinations injected monthly produce regular cyclicity. The approach seems to be better than long-acting progestins alone since there is less spotting or no amenorrhoea. Remembering the date for injection becomes easier. A visit to the clinic for injection every month ensures a proper follow-up. However, there is the inconvenience of more frequent injections and possible side-effects of the oestrogen component need to be checked.

Two oestrogen-progestin formulations are currently in use: (i) a combination of 75-150 mg dihydroxyprogesterone acetophenide and 5-10 mg oestradiol enanathate, used primarily in Latin America; and (ii) a combination of 250 mg 17-hydroxyprogesterone caproate and 5 mg oestradiol valerate, used only in China.

In clinical trials with 150 mg dihydroxyprogesterone acetophenide and 10 mg oestradiol enanthate involving nearly 23,000 cycles in 2,400 women, no pregnancies were reported. The drop-out was between 8-26 per cent due to bleeding problems (Benagiano and Primiero, 1983). Return of ovulation may be slightly delayed. Because of the concern about accumulation in the body of the oestrogen over time, half doses of oestrogen have been tried. These lower doses prevent pregnancy effectively but severely disrupt menstrual patterns (Recio ***et al.*** 1986).

In China, a formulation called injectable Number 1 accounts for less than 1 per cent of all contraceptive users. The major disadvantage of this method is a very short cycle and prolonged bleeding.

WHO is conducting trials on two new monthly injectables along with Family Health International in three countries: (i) Cycloprovera, a combination of 25 mg DMPA and 5 mg oestradiol cypionate; and (ii) HRP 102, a combination of 50 mg northindrone enanthate (NET-EN) and 5 mg oestradiol valerate.

Preliminary results in a study of 2400 women in three countries show that both formulations are highly effective, both preparations induced bleeding patterns like normal menstrual cycles and side-effect have been minor (Hall 1987).

TABLE 7
CHARACTERISTICS AND STATUS OF MONTHLY INJECTABLES
AS OF MARCH, 1987

Hormone	Development and Testing	Duration of Action	Animal Trials	Human Trials Phase I	Phase II	Phase III	Estimated availability
Cycloprovera	WHO, HRP	1 Month	Completed	Completed	Underway in 3 sites 150 women	Underway in 17 sites on 1200 women	Expected in early 1990s
HRP 102	WHO, HRP	1 month	Completed	Completed	Underway in 4 sites 200 women	Underway in 17 sites on 1200 women	Expected in early 1990s

Microspheres and Microcapsules

Injectable microspheres and microcapsules consist of a biodegradable co-polymer and one or more hormones. These microspheres and microcapsules may protect against pregnancy for one, three or six months depending on the amount and daily release of hormones. The carrier of these injectables is poly (dl-lactide-co-glycolide). Progestins can be dispersed in the polymeric particle (Microsphere; Fig. 3) or contained in the core of the particle (Microcapsule). With both systems, the hormone is released first by leaching or by diffusion through the carrier and later by erosion of the carrier. A 3-month dose of injectable norethindrone (NET) microspheres usually contains particles consisting of 50 per cent hormone and ranging in size from 0.06 to 0.1 mm in diameter (Beck and Pope, 1984). For an injection, microspheres are loaded into a syringe followed by a sterile suspension fluid and the total volume of about 2.5 ml is injected into the buttocks with a 21 gauge needle. Various preparations of the injectable microspheres are being tested for contraception in women. The most promising hormones used in the microspheres are either norethindrone or a new progrestin, norgestimate.

Norethindrone containing microspheres tested in about 200 women with different formulations of 3-month injections have prevented pregnancy and caused very few side-effects other than menstrual irregularities. The 3-month injections containing 75 mg of norethindrone release on an average 0.48 mg norethindrone per day, as compared to 0.5 to 1 mg in combined oral contraceptives.

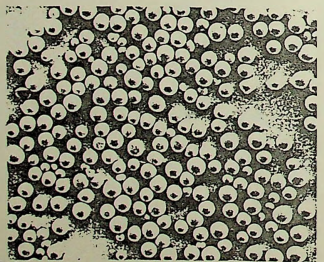

Fig 3. In clinical trials norethindrone microspheres prevent pregnancy for three months. Microspheres are .06 to 0.1 mm in diameter. The smaller microspheres release hormone faster. (Stolle Research Corporation)

Irregular menstrual bleeding is the only common side-effect and only a few complained of mild headaches or nausea. No changes have been observed in blood pressure, haemoglobin, serum lipoproteins, triglycerides, or glucose metabolism (Bech and Pope, 1984). The reversibility is rapid and most women ovulate within two months (Rivera *et al.* 1984).

A one month injection with 15 or 30 mg NET has been tested in 30 women in Mexico. Animal studies in baboons with microspheres of NET and ethinyl oestradiol indicate very little irregular bleeding and very slight endometrial changes. Clinical trials with progesterone microcapsules containing 275 mg progesterone on 10 women demonstrated good promise (Table 8).

In China, monthly injections of microcapsules containing 15 mg megestrol acetate and 5 mg of oestradiol valerate in 434 women were found to be effective with a pregnancy rate of 1.1 per HWY. Spotting occurred in only 3 per cent of menstrual cycles and only 9 per cent of cycles were either longer than 36 days or shorter than 20 days (Han and Xiao, 1985).

Subdermal Implants

There are two kinds of implants made of poly dimethyl siloxane (Sialstic) or other polymer-based rods or capsules that are placed under the skin by a trocar. Depending on the amount and type of progestin, the number of implants to be inserted vary as per desired duration of action of the drug. One kind of implant is nonbiodegradable and the other is biodegradable. In the last two decades a number of progestogens have been tested. The most promising are ST-1435, norgestrienone and levonorgestrel (Roy *et al.* 1984). ST-1435 using 1-5 capsules lasted only for six months and the pregnancy rate was 1 or less per HWY (Coutinho *et al.* 1981). Norgestrienone (R-2010) implants last from 18 to 24 months with 6 capsules but the pregnancy rate was 3-5 per HWY.

Nonbiodegradable Implants: The nonbiodegradable implants developed by the Population Council have undergone widespread clinical trials involving more than 44,000 women in 31 countries (Population Council, 1986). The implant favoured by the Population Council, named Norplant, contains levonorgestrel and proved to be highly effective, safe and liked by its users. By 1987, a 6-capsule Norplant system had been approved for marketing in seven countries - Finland, Sweden, Indonesia, Thailand, Ecuador, Dominican Republic and Colombia.

Norplant implants come in two forms (Fig. 4). The first, called simply Norplant, consists of six hollow silastic capsules. Each capsule is 34 mm long, with a diameter of 2.4 mm and contains 36 mg levonorgestrel. The ends of the capsules are sealed shut with silastic adhesive. This is highly effective in preventing pregnancy for five years. The other form, called Norplant-2, consists of two solid silastic rods, each 44 mm long and 70 mg levonorgestrel is dispersed in the matrix of each rod. Norplant-2 is highly effective for at least three years. This system was approved in Finland in 1987.

TABLE 8

CHARACTERISTICS AND STATUS OF INJECTABLE MICROSPHERE AND MICROCAPSULE CONTRACEPTIVES AS OF MARCH, 1987

Hormone	Development and Testing	Duration of Action	Status of Animal Trials	Status of Human Trials			Estimated availability
				Phase I	Phase II	Phase III	
Norethindrone microspheres	Stolle Research & Development Corporation Family Health International	3 months	Completed	Completed	Underway at 8 sites in US Mexico, Chile & Italy with 65 & 100 mg formulations in 160 women	Planned with 65 mg formulation in 1200 women	Early 1990s
		6 months	Completed	Completed in Mexico & US with 200 mg formulation	-	-	Late 1990s
		1 month	Completed	Completed in Mexico with 15 mg & 30 mg formulations in 30 women	-	-	Mid 1990s
Norgestimate Microcapsules	Ortho Pharmaceutical & CONRAD	3 months	Completed	Underway in US with 50 mg formulation	-	-	Mid 1990s
Progesterone Microcapsules	Stolle Research & Devpt. Corpn.	3 months	Completed	Underway in Chile & US	-	-	Late 1990s
Levonorgestrel Microspheres	Stolle Research & Devpt. Corpn.	3 months	Completed	Approved to start in US	-	-	Late 1990s
Norethindrone ethinyl estradiol Microspheres	Stolle Research & Devpt. Corpn.	3 months	Completed	Approved to start in US with 30 mg NET & 5 mg EE	-	-	Late 1990s

Fig. 4. Norplant implants release levonorgestrel.

The progestin in the implants diffuses through the silastic membrane at a steady and slow rate. Within 24 hours, the levels in blood plasma are high enough to prevent ovulation (Bardin and Sivin, 1985). The average daily release ranges from 50 to 80 µg in the first year and declines to 30 to 35 µg over the next five years (Diaz *et al.* 1982).

Insertion and removal of Norplant implants require a minor surgical procedure under local anaesthetic and a small incision. Removal is more difficult than insertion. The best time for insertion is during menstruation to ensure that the woman is not pregnant. The implants are inserted under the skin. Infections and other complications after insertion are rare (3 per 1000; Sivin *et al.* 1983). With the exception of one trial in India (ICMR, 1985) capsules and rods are rarely expelled. The removal of 6 implants takes about 15 to 20 minutes. Generally, the removal is comparatively easy if insertions are made properly.

Capronor (long capsule at left) and contraceptive pellets are both long-acting implants that dissolve in body tissue and do not need to be removed. The special inserter can be used with either.

TABLE 9

CHARACTERISTICS AND STATUS OF NOBIODEGRADABLE IMPLANTS
AS OF MARCH, 1987

Delivery System	Development & Testing	Hormone	Duration of Action	Status Animal Trials	Status Human Trials Phase I	Phase II	Phase III	Availability
Norplant (6 capsules)	Population Council	Levonor-gestrel	5 years	Completed	Completed	Completed	Completed or under way in 31 countries	Approved in 7 countries
Norplant-2 (2 rods)	Population Council	Levonor-gestrel	3 years	Completed	Completed	Completed	Under way in 9 countries	Approved in Finland
1 Rod*	Population Council	ST-1435	2 years	Partially completed	Completed	Completed	Planned	Mid 1990s
1-Rod*	Population Council Organon	3-Keto Deso-gestrel	2½/2-4 years	Completed	Completed	Under way in 3 countries	Planned	Early 1990s

*Trade name not yet chosen

Norplant provides almost complete protection against pregnancy. In the first five years of use of the Norplant 6-capsule system, the chances of pregnancy are less than one per HWY. This rate is lower than for oral contraceptives, IUDs or barrier methods. On-going international trials show that Norplant-2 is as effective as the 6-capsule system for the first three years of use (ICMR, 1986). After three years, a high number of pregnancies occurred in a large 5-country trial.

Norplant suppresses ovulation in at least half of the menstrual cycles (Bardin and Sivin, 1985). Whenever ovulation occurs, the levonorgestrel is effective due to its action on cervical mucus which becomes thick, scanty and impermeable to spermatozoa. The cyclic development of the endometrium is also suppressed (Croxatto *et. al.* 1984). About 60 per cent of women using Norplant suffer from irregular menstrual bleeding during the first year (Sivin *et al.* 1983). Among 116 women using the 6-capsule system for five years, the average number of days of bleeding and spotting per year dropped from 92 in the first year to 70 in the fifth year (five per cycle). Amenorrhoea is less common than prolonged bleeding or spotting. No serious reproductive side-effects have been reported so far. Transient ovarian cysts have been found in 10 per cent of users (Diaz *et al.* 1982). The cysts however, regress spontaneously within six weeks.

The contraceptive effect of Norplant is reversed rapidly after removal of the implants and the infants are free from any after-effect of the progestin. Only minor changes have been observed in liver function, carbohydrate metabolism, blood coagulation, blood pressure, immunoglobulins, serum cortisol, urea nitrogen, uric acid, minerals and body weight but all remained within the normal range.

Biodegradable Implants: The problems associated with the removal of Norplant implants led to the development of biodegradable implants. These implants degrade in situ while releasing the impregnated progestins and in the process obviate the requirement of removals. However, once the carrier begins to dissolve, it cannot be removed.

The biodegradable implants undergoing clinical trial at present include Capronor and Norethindrone pellets. Capronor consists of a biodegradable capsule made of the polymer only (E-caprolactone) containing the progestin levonorgestrel. Norethindrone pellets are made of 15 per cent pure cholesterol and 85 per cent norethindrone (NET).

Capronor: Current trials with this biodegradable capsules (Fig. 5) involve implants that are less than 0.24 cm in diameter and either 2.5 cm or 4 cm long. The shorter capsule contains 16 mg and the longer 26 mg levonorgestrel. In both capsules the progestin is suspended in ethyl oleate. Studies in rabbits and monkeys suggest that the contraceptive protection would last for about 18 months and longer. The polymer carrier remains largely intact for 18 to 24

months and can be removed easily during this period, if necessary. However, it is not completely absorbed for several years. The phase II clinical trials comparing the 2.5 and 4 cm capsules began in early 1987 and are being conducted by US National Institute of Child Health and Human Development (NICHHD), the World Health Organization (WHO) and the Indian Council of Medical Research (ICMR).

In the preliminary study on eight women in the US, none reported bleeding between menstrual periods, average length of the cycle was four days shorter and there was no change in blood pressure or blood biochemistry, including lipids. The capsules did not cause inflammation at the insertion site (Ory *et al.* 1983)

Norethindrone Pellets: Each of these pellets contains 35 mg NET which is released as the pellets gradually biodegrade. The size of each pellet is little larger than a grain of rice (Gupta *et al.* 1984; Singh *et al.* 1985). Preliminary trials have been conducted with two, three and four pellets in over 100 women in four countries. The release of the progestin was fairly constant (Singh *et al.* 1985).

TABLE 10

HORMONE RELEASE RATES AND NUMBER OF PREGNANCIES WITH TWO, THREE AND FOUR NET PELLETS

No. of Pellets	Mean Daily Release (ug)	No. of Women	No. of Pregnancies
2	11± 2	50	3 at 6 months
3	150± 7	51	2 at 12 months
4	213± 9	30	0 at 12 months

TABLE 11

CHARACTERISTICS AND STATUS OF BIODEGRADABLE IMPLANTS AS OF MARCH, 1987

Delivery	Development & Testing	Hormone	Duration of Action	Status of Animal Trial	Status of Human Trial Phase I	Phase II	Phase III	Availability
Capronor	Research Triangle Institute	Levonor-gestrel	18 months	Completed	Completed	Began in 1987 in 6 countries with 250 women		Mid 1990s
NET Pellets	Population Council Endocon Inc.	Norethin-drone	1 year	Completed	Completed with 2 pellets.	Completed in 3 countries with 3 or 4 pellets in 81 women		Mid 1990s

The 4-pellet regimen appears to provide a high level of protection against pregnancy.

One of the main drawbacks of these pellets is menstrual irregularity. Lengthy menstrual period, spotting as well as amenorrhoea were encountered in women who had these pellets inserted.

Vaginal Rings (Fig. 6)

Steroids can be absorbed through the vaginal mucosa which pass directly to the veins draining into the inferior vena cava and, as with injectables and implants, bypass the liver on their first pass. A number of progestogens have been made into sustained release systems that can be left in place in the vagina for three weeks and removed for one, during which menstruation occurs (Fraser and Weisberg, 1981; Sivin ***et al***. 1981). A poly siloxane ring is impregnated with levonorgestrel, progesterone or a combinatioin of progestin and estrogen.

With the vaginal ring, the cycle control is usually good. The ring sometimes gives rise to a discharge and the acceptability of inserting such a ring, leaving it in place for three weeks and then removing it, cleaning it and storing for one week has not been extensively investigated.

Research is most advanced on a ring developed by WHO that releases 20 µg levonorgestrel per day. This ring is designed to stay in the vagina for three months. The inner core of the ring contains 6 mg of levonorgestrel mixed with silastic and an outer shell of silastic alone.

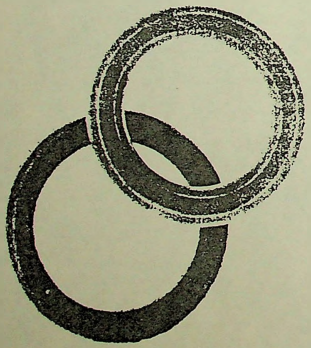

Fig. 6. **Two vaginal rings (shown actual size) release hormone for 3 months. The upper ring contains norgestrel; the lower, progesterone.**

The overall diameter of the ring is 55.6 mm and cross-sectional diameter is 9.5 mm. The ring prevents ovulation in at least half of the cycles and thickens the cervical mucus. However, this ring was found to be less effective than implants or injectables. In a multicentric trial involving about 1000, women there were 25 pregnancies in one year, the rate being 3.5 per HWY (WHO Annual Report, 1985). About 8 per cent of women stopped using the ring because of vaginal discharge, irritation or infection and about 4 per cent, because of expulsion.

Another ring contains the natural hormone progesterone designed especially for breastfeeding women to prevent exposure to synthetic hormones which may alter the composition or quality of breast milk. Currently, WHO and Population Council are testing rings releasing 5 or 10 mg progesterone daily.

The Population Council is working on several rings that deliver both progestins and oestrogens. Preliminary studies with a ring releasing 400 µg norethindrone acetate and 40 µg ethinyl estradiol daily stopped ovulation in all of the ten women recruited for the study and caused very little irregular bleeding. The Population Council also plans to test vaginal rings with two other progestins, ST-1435 and levonorgestrel acetate, either alone or in combination with ethinyl estradiol.

The rings appear to have several disadvantages for large scale use among the population.

Medicated IUDs

The success of IUDs depended on their surface area and the larger was the device, the better it protected a woman against pregnancy. However, the larger the device, the more were the complaints and the higher the expulsion and removal rates due to bleeding or pain. It was in response to this problem that the medicated devices were designed. These devices work on the principle that the plastic is used as a carrier for chemicals which work to prevent pregnancy. The first medicated device was developed by Zipper ***et al***. 1969, in which 200 sq. mm of copper surface was exposed by wrapping copper wire around a T device. A low concentration of copper ions is released into the uterine cavity and there is a direct relation between the area of copper exposed and the contraceptive efficacy. Copper ions have no inhibitory effect on ovulation or fertilization but may be spermicidal and certainly stimulate migration of white blood cells into the uterine cavity. This particular device known as TCu 200 is being used in the National Programme in India. With this device, pregnancies were effectively prevented for 2-3 years. The copper was found to be released at the rate of 45 µg daily and the amount of copper in the device could be exhausted by six years. However, fragmentation of copper and deposition of calcium were responsible for decline in effectiveness beyond three years. To prevent the fragmentation and loss of effectiveness, various surface areas of copper with or without other metals like silver were

37% had used a Hulka clip, and 21% had used a tubal ring. Four pregnancies were confirmed, all occurring between two and seven years following VSC: three ectopic pregnancies in the electrocoagulation group and one uterine pregnancy in the Hulka clip group (no pregnancies occurred in the tubal ring group). Because pregnancies occurred as late as seven years following VSC, the authors concluded that short-term failure rates for female VSC probably do not represent actual failure rates. Other conditions often thought to be sequelae of VSC, including adnexal masses, pelvic infection, and various conditions requiring hysterectomy, could not be linked to VSC or to the use of a specific occlusion technique.

Long-acting Progestins

Klavon, S.L. and G.S. Grubb. Insertion site complications during the first year of NORPLANT® use. Contraception, Vol. 41, No. 1, January 1990, pp. 27-37.

First-year clinical trial data on insertion site complications among 2,674 NORPLANT® acceptors in seven countries showed that infection and expulsion rates were low, but that a substantial proportion of insertion-related complications occurred after the first two months of use. Complication rates varied widely among countries and between clinics within a country. At one year, complication rates were: insertion site infection, 0.8%; expulsion, 0.4%; local reaction, 4.7%. While most complications occurred within 60 days of insertion, some 35% of insertion site infections and 64% of expulsions occurred after 60 days; about two-thirds of these infections and expulsions were among women without insertion site complications during the first 60 days. Possible causes of later infection were (1) trauma to the insertion site causing it to open or (2) change in the immunologic environment of the implants. The authors recommended that implants be removed when infection occurs: of 16 women with infections who did not have the implants removed immediately, half eventually had them removed.

Paul, C. et al. Depot medroxyprogesterone (Depo-Provera) and risk of breast cancer. British Medical Journal, Vol. 299, September 23, 1989, pp. 759-762.

This New Zealand population-based case-control study found no overall increase in risk of breast cancer with use of the three-month injectable contraceptive Depo-Provera (DMPA), but found increased risks in users who: (1) were diagnosed with breast cancer before age 35, (2) had used DMPA for at least two years before age 25, and (3) had used it recently. Cases consisted of 891 women age 25-54 with recently diagnosed breast cancer selected from the National Cancer Registry; controls consisted of 1,864 women randomly selected from electoral rolls and matched to cases by age. DMPA had been used by 12.3% of cases and 13.5% of controls. The relative risk of breast cancer (adjusted for confounding variables) with any duration of use was 1.0. In women age 25-34, the relative risk was 2.0. For women who first used DMPA before age 25, the relative risk was 1.5. In both groups, risk was higher in those who used DMPA for six years or longer. The relative risk for women who last used DMPA within five years was 1.6; the highest relative risk in these women was associated with the shortest duration of use. For all categories of duration of use, risk declined with increasing time since last use. The authors determined that a possible explanation for this finding is that DMPA increases the risk of breast cancer only during the first few years after exposure, suggesting that it may act as a promoter during late stages of carcinogenesis. The authors commented that these results could be interpreted to mean that DMPA has an initial harmful effect, followed by a protective effect, and noted the need for additional research to clarify the findings.

while 19 women said a WPC-333 was less convenient and 6 said it was less comfortable than a male condom, some 80% said they would advise other sex workers to try it. The women were counseled concerning their risk for AIDS and how to use the new device, then given unlubricated WPC-333s, lubricant, and male condoms and allowed to decide which device to use, if any. All women tried the WPC-333. After two weeks and 247 episodes of vaginal intercourse, they reported their use of the devices: no device, 34%; male condom, 35%; WPC-333, 32%. The women's principal objections to the WPC-333 were that it was too big (17 cm) and, since it needed to be lubricated, was messy and inconvenient. Partner reaction to the WPC-333 varied: half of the women said all of their partners objected to it, 40% said partner reaction was mixed, and 10% said all of their partners approved of it. No rips or tears in the WPC-333 were reported. Researchers plan to repeat the study at the same site using 15 cm prelubricated WPC-333s.

Long-Acting Progestins

Zimmerman, M. et al. Assessing the acceptability of NORPLANT® implants in four countries: findings from focus group research. Studies in Family Planning, **Vol. 21, No. 2, March/April 1990, pp. 92-103.**

This qualitative research project conducted in four countries where NORPLANT® contraceptive implants had been available for at least five years produced new data and confirmed previously reported findings on attitudes, perceptions, and experiences related to NORPLANT®. Focus group discussions and in-depth interviews were held in the Dominican Republic, Egypt, Indonesia, and Thailand with potential acceptors, current NORPLANT® users, discontinuers, husbands of women in these three groups, and service providers. Perceived advantages of NORPLANT® use were similar in all countries and included ease of use; high, long-lasting effectiveness; reversibility; and few side effects compared with other methods. Potential acceptors in all countries were concerned about pain during insertion and removal. In all countries there was evidence that some women did not have access to removal services for a variety of reasons; for example, some providers were reluctant to remove an expensive method after short-term use, women migrated to areas that lacked trained personnel, etc. Among the major findings were (1) service providers need additional technical training in insertion, counseling, and removal and (2) additional and better information on NORPLANT® is required for various audiences, including friends and family of potential users.

Pregnancy Termination

Grimes, D.A. et al. Predictors of failed attempted abortion with the antiprogestin mifepristone (RU 486). American Journal of Obstetrics and Gynecology, **Vol. 162, No. 4, April 1990, pp. 910-917.**

This U.S. study found three factors significantly associated with likelihood of failed abortion with RU 486 use: drug regimen used, patient body mass, and ß-human chorionic gonadotropin (ß-hCG) level before treatment. The analysis included data for 271 women who received various regimens of RU 486 for early pregnancy termination (less than 50 days amenorrhea) in research trials from 1984-1989. Thirteen different regimens were used, grouped into three categories for analysis. The regimen used was the most powerful predictor of failed abortion: women who received 600 mg of RU 486 (single or multiple doses with or without prostaglandin) (118 women) were significantly less likely to experience failure compared with women who received various doses over 7 days

Long-acting Progestins

Singh, K. et al. A three-year clinical evaluation of NORPLANT-2® rods in Singapore. Advances in Contraception, **Vol. 6, No. 2, June 1990, pp. 63-69.**

Three-year data for 100 NORPLANT-2® users in Singapore showed that, among these women, NORPLANT-2® was highly effective, safe, and well-accepted. Women in the study were age 18-40, had demonstrated fertility (at least one birth), and were at risk of pregnancy. All 100 women were followed for the full three years of the study. There were no accidental pregnancies. Twenty-six women requested removal: 14 because a pregnancy was desired, 8 for bleeding disturbances, and 4 for other medical reasons. Prolonged bleeding was the most common side effect. All types of bleeding disturbances diminished over time; incidence of disturbances after three years was: prolonged or frequent bleeding, 0%; infrequent bleeding, 4.1%; and amenorrhea, 3.5%. Of the 14 women who stopped using NORPLANT-2® to become pregnant, 7 conceived within 3 months of removal, 4 decided not to become pregnant and adopted another contraceptive method, and 3 failed to become pregnant during the study period.

Intrauterine Devices

Chi, I. et.al. Is the Copper T 380A device associated with an increased risk of removal due to bleeding and/or pain? An analysis. Contraception, **Vol. 42, No. 2, August 1990, pp. 159-169.**

Analysis of 12-month data from four randomized comparative clinical trials showed that the Copper T (TCu) 380A was at least as effective as the comparative device (TCu 200, TCu 220C, Multiload 250, or Lippes Loop D) and was no more likely to be removed for bleeding and/or pain. Data were collected at four sites (two in Latin America and two in Asia) between 1984 and 1987 and involved 1,181 insertions performed at least 42 days after the last pregnancy. At all sites, the 12-month accidental pregnancy rate was consistently lower for TCu 380A users than for users of the comparative device. The difference in pregnancy rates was statistically significant only when the TCu 380A and TCu 200 were compared. There was no statistically significant difference in any of the trials between the TCu 380A and the comparative devices in removal rates for bleeding and/or pain: the rates were (1) TCu 380A, 6.6% and TCu 200, 3.2%; (2) TCu 380A, 0.9% and TCu 220, 1.5%; (3) TCu 380A, 1.5% and Multiload 250, 2.0%; and (4) TCu 380A, 3.1% and Lippes Loop, 4.9%. None of the findings changed substantially when data for 31 nulligravid women were excluded from the analysis.

Sinei, S.K.A. et al. Preventing IUCD-related pelvic infection: the efficacy of prophylactic doxycycline at insertion. British Journal of Obstetrics and Gynaecology, **Vol. 97, No. 5, May 1990, pp. 412-419.**

A study of 1,655 Kenyan women followed for one month after IUD insertion found that a single dose of the antibiotic doxycycline (200 mg) given orally at least one hour before the insertion was associated with a reduced rate of unplanned clinic visits for IUD-related problems. Women in the study had requested IUD insertion at a Nairobi hospital clinic between December 1984 and January 1986. Those who did not have pelvic inflammatory disease (PID), had not used antibiotics within the last two weeks, and otherwise met the study's inclusion criteria were randomly assigned to receive doxycycline (827 women) or a placebo (828 women). The rate of unplanned clinic visits within one month of insertion for IUD-related problems was significantly lower in the doxycycline-treated group (8.9%) than in the placebo-treated group (13.0%). The rate of PID one month after

Population Reports

Decisions for Norplant Programs

Norplant is new. After decades of careful development and testing, Norplant implants are taking their place as the newest choice among family planning methods. Family planning programs now face important decisions about whether to offer Norplant and how to offer it in ways that meet clients' needs.

Norplant is already becoming popular. To date the implants are widely available or their use is expanding rapidly in 14 countries, including Indonesia, Thailand, and the US. An estimated 1.8 million women have used the method. Regulatory agencies in 23 countries have approved the product.

What Is New About Norplant?

The unique feature of Norplant is how it is used. Six flexible capsules, each about the size of a paper match, are placed just under the skin of a woman's upper arm. For five years the capsules steadily and slowly release a hormone that prevents pregnancy. Only one woman in every 500 becomes pregnant in the first year of Norplant use—a first-year rate as low as for any temporary family planning method. Over five years, one in every 25 women becomes pregnant. When the capsules are removed, a woman's normal fertility returns quickly. In the meantime, the method is easy to use: the user needs to do nothing more to avoid pregnancy.

Norplant implants are likely to suit some women especially well. Norplant may particularly suit women of all ages who do not want to become pregnant for several years, women

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Published with this issue:
"Norplant at a Glance" fact sheet for policy-makers; "Guide to Norplant Counseling" for providers

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who want no more children but do not want or cannot obtain sterilization, women who want the effectiveness of a hormonal method without the side effects of estrogen, women who do not want to worry about remembering a daily pill, and women far from dependable supplies of contraceptives.

Like every other family planning method, Norplant implants also have drawbacks. Like voluntary sterilization and intrauterine devices (IUDs), implants depend on specially trained personnel, who must insert and remove them. Like progestin-only injectables and minipills, they change menstrual patterns in most women. Also, they cost donor organizations and developing-country family planning programs US$23 per set, not including training, salaries, and other service costs for counseling, insertion, and removal. In the US, a set of Norplant capsules costs $350.

Deciding on Norplant

Because Norplant use depends on providers, a program that decides to offer Norplant makes a special commitment to meeting users' needs. These needs include a free and informed choice among methods, including Norplant; mass-media information and face-to-face counseling that help clients understand Norplant and decide whether it will suit them; services that do not create unneeded barriers to using Norplant by requiring unnecessary tests, procedures, or eligibility criteria and yet give adequate attention to clients who want more attention; help on hand when users need advice; and convenient services when they want the capsules removed. Programs must decide whether they can afford the necessary high quality of care, keeping in mind that in the long run poor care is more costly and more wasteful than good care.

Introducing Norplant

For programs that choose to offer Norplant, a clear consensus on its role is important. Managers in each program need to assess what are the most important characteristics of the new method, who might find Norplant most appealing, and what implants offer compared with other available methods—a planning process known as positioning. The role of Norplant in a program may depend greatly on what other methods, such as voluntary sterilization, IUDs, and oral contraceptives, are available and popular.

Program managers may want to position Norplant for women who want long-term, reversible contraception. At the same time, providers should not withhold Norplant or any other method from any client who can use it. Nor should they pressure any client into choosing it or continuing to use it against her wishes. In the long run programs are seeking successful users of family planning, and the most successful users are satisfied clients.

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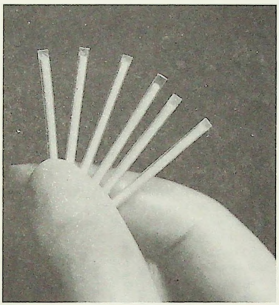
What Is Norplant?

Norplant* implants are a new contraceptive method. Norplant consists of six flexible capsules, each about the size of a paper pocket match (see photograph, this page). The capsules are inserted under the skin usually on the inside of a woman's upper arm. The implanted capsules prevent pregnancy by releasing the hormone levonorgestrel into the blood stream at a slow, steady rate.

Norplant has many advantages. It is:

- Very effective at preventing pregnancy;
- Approved for five years of use;
- Reversible at any time by having the capsules removed;
- Free from estrogen side effects;
- Easy to use, with nothing to remember each day or at the time of intercourse;
- Convenient because there is no need to obtain supplies periodically.

The chief disadvantages of the method to the user are that she must depend on a health care provider to insert and remove the capsules and that the hormone, a progestin, changes menstrual bleeding patterns.



Norplant implants consist of six small caspules. Inserted under the skin of a woman's upper arm, the capsules prevent pregnancy for up to five years.

More than 1.8 million women in 51 countries have used Norplant. Several thousand women have used Norplant in clinical and pre-introduction trials conducted by, or in association with, the Population Council, developer of Norplant (151, 171). Implants are now widely available or their use is rapidly expanding in 14 countries including Indonesia, Thailand, and the United States, where hundreds of thousands of women use Norplant. In nine other countries regulatory agencies have approved Norplant, but it is not yet widely available, and three countries without drug approval processes offer Norplant in family planning programs. In these and other countries family planning officials are assessing Norplant and considering how to introduce it.

Norplant expands the range of family planning choices available to women. As with any method, its unique combination of features will serve some women particularly well. Women who want a long-term, reversible method may especially like Norplant. Women who have had, or are likely to have, difficulties with the intrauterine device (IUD) or the estrogen in combined estrogen-progestin oral contraceptives may want to try Norplant. Also, women who do not want to have a pelvic procedure can choose Norplant as an alternative to an IUD. As with other hormonal methods, Norplant can be used by women of any age and by women who have never been pregnant.

A new family planning method offers an opportunity to serve more people who want to control their fertility. Taking advantage of this opportunity requires: (1) good medical care during insertion, removal, and the management of side effects, (2) thorough, high-quality counseling, and (3) publicity that appeals particularly to women who might want Norplant and that informs them of available services (see pp. 16–17). Program managers must plan all of these activities before they introduce Norplant.

Cost is an issue in deciding how, or whether, to introduce Norplant. Both the costs of introducing the method and of providing the implants are higher than those of most other methods (see p. 15). Introductory costs include training health care providers to insert and remove capsules and to counsel women. Continuing costs include the salaries and infrastructure for the providers and the cost of the implants themselves, as well as continuing training. Each set of implants costs US$23 to nonprofit groups and public organizations in developing countries and to donor agencies. This commodity cost is much higher than the cost of an initial supply of other temporary methods. Because Norplant can be used for as long as five years, however, its cost per year may not be much more than that of some other methods (see Table 1). The cost per year for an individual woman depends on how long she uses Norplant. Some women will decide to have their implants removed before five years of use, and these decisions must be honored. Program managers must be sure that they can afford to introduce and provide Norplant in a way that does not compromise their clients' right to make their own health care decisions.

The Implant Method

Norplant implants combine materials used in other medical products into a new contraceptive delivery system. Norplant consists of a set of six capsules filled with the progestin levonorgestrel, which has been used in oral contraceptives for more than 20 years. The capsules are made of medical-grade Silastic tubing, a material like that used in medical drainage tubes and prosthetic devices since the 1950s. Each capsule is 34 mm long and 2.4 mm in diameter (151). Through a small incision, the capsules are inserted one by one in a fan-shaped pattern just under the skin.

Each capsule contains 36 mg of levonorgestrel in crystalline form (151, 184). The six capsules together initially release approximately 85 µg per day, decreasing to 50 µg per day by 9 months of use, to 35µg per day at 18 months, and then to 30 µg per day during the third, fourth, and fifth years of use (151, 219).

How Norplant works. The levonorgestrel in Norplant prevents pregnancy in several ways. It makes cervical mucus thicker and reduces the amount produced. Sperm have difficulty moving through such thick and meager mucus, and therefore few sperm pass through the cervical canal to reach the uterus (32, 44, 151, 219). Also, the progestin suppresses ovulation in at least half of menstrual cycles (31). Recent

*NORPLANT is the registered trademark of The Population Council for levonorgestrel subdermal implants.

Table 1. Norplant Implants Compared with Other Methods

Method	Lowest Expected/ Typical First-Year Pregnancy Rate (per 100 Women)	Continuation Rate 1 Year/5 Years	Reversibility	Resupply Frequency	Dependence on Specially Trained Service Provider	Most Common Side Effect	Approximate Commodity Cost for 3.5 Years[a] (US$)[b]
Norplant implants	0.2/0.2[c]	82–95%/ 25–78%[d]	Immediately after removal	Every 5 years	High	Changes in menstrual bleeding	US AID: $23[e] IPPF: $29[e] UNFPA: $23[e]
Tubal ligation	0.2/0.4[f]	—	Surgery required; success not guaranteed	None	High	Postoperative complications	—
Vasectomy	0.1/0.15[f]	—	Surgery required; success not guaranteed	None	High	Some pain & swelling; postoperative complications	—
Intrauterine device (IUD)	0.8[f]/2.0–3.4[g]	75–95%/ 33–41%[h]	Immediately after removal	Every 8 years	High	Increased bleeding and uterine pain	US AID: $1[i] IPPF: $.80[i] UNFPA: $.70[i]
Depo-Provera injectable/ Noristerat injectable	0.3/0.3[f] 0.4/0.4[f]	70%[f]/NA	Usually several months after last injection	Depo-Provera: Every 3 months Noristerat: Every 2 months or 12 weeks	Moderate	Changes in menstrual bleeding	IPPF: $14/$27 UNFPA: $8/$14
Combined oral contraceptives	0.1[f]/5.9[g]	73%[f]/NA	1–3 months after discontinuation	One month per packet; multiple packets available	Low	Nausea	US AID: $6–$11 IPPF: $8–$24 UNFPA: $6-$7
Condoms	2/12[f]	64%[f]/NA	Immediate	Each act of intercourse; can be obtained in multiples	Low	None	US AID: $17[j] IPPF: $11–$28[j] UNFPA: $9[j]
Spermicide tablets	3/21[f]	43%[f]/NA	Immediate	Each act of intercourse; can be obtained in packages of 6–20	Low	Local allergic reaction	IPPF: $30–$43[j] UNFPA: $33–$43[j]
Diaphragm + spermicidal cream	6/18[f]	57%[k]/NA	Immediate	Spermicide at each act of intercourse; available in tubes of various sizes	Low	Urinary tract infection	IPPF: diaphragm $6.50, spermicide $32–$66[i]
Natural Family Planning	1–9/20[f]	67%[f]/NA	Immediate	None	Moderate	None	None

NA = Not available

[a] *Average duration of Norplant use in clinal trials*

[b] *Price to United States Agency for International Development (US AID) and United Nations Population Fund (UNFPA): commodity cost only. Price from International Planned Parenthood Federation (IPPF) to affiliates: includes commodity, shipping, and shipping insurance.*

[c] *Source: Population Council (174)*

[d] *Source: Sivin (219)*

[e] *Trocar not included*

[f] *Source: Trussell et al. (240). Except for injectables, rates are largely from English-speaking developed countries; developing-country rates not available.*

[g] *Source: Moreno & Goldman (135)*

[h] *Source: Sivin et al. (228)*

[i] *For TCu-380A IUD*

[j] *Assumes 150 units = 1 couple-year of protection*

[k] *Source: Edelman (61)*

research suggests that, even when ovulation occurs, endocrine dysfunction would usually prevent fertilization of the egg if sperm were to reach it (72). The constant low levels of levonorgestrel also may suppress the growth of the endometrial lining of the uterus, thus preventing implantation (46, 200, 201). A recent study of one menstrual cycle per woman found no sign of fertilization among 32 Norplant users, but 9 of the 20 women in a control group who wanted to become pregnant produced the glycoprotein human chorionic gonadotropin (hCG), which indicates the presence of a fertilized egg within nine days after conception. Six of these women in fact were pregnant (193).

Features That Women Most Appreciate

Women who have used Norplant like the fact that the implants are easy to use, effective, and reversible.

Easy to use. Once the implants are put into a woman's arm, she needs to take no further steps to prevent pregnancy for up to five years. Thus Norplant is particularly appropriate for women who do not want to worry about remembering to take a pill every day or to use condoms, spermicide, or a diaphragm at the time of sexual intercourse.

Effective. Norplant is one of the most effective contraceptive methods. The Population Council has compiled annual pregnancy rates and the cumulative 5-year pregnancy rate for 2,670 woman in 13 countries (174, 224):

Annual Pregnancy Rates and 5-Year Cumulative Pregnancy Rate Among Norplant Users

Year	*No. of Women Completing Year*	*Rate per 100 Women*	
Year 1	1,954	0.2	or 1 in 500
Year 2	1,379	0.5	or 1 in 200
Year 3	1,067	1.2	or about 1 in 80
Year 4	743	1.6	or about 1 in 60
Year 5	476	0.4	or 1 in 250
5-year cumulative		3.9	or 1 in 25

The first-year pregnancy rate of 0.2 per 100 women for Norplant is lower than the first-year rates for injectables, oral contraceptives, and most other contraceptive methods (129, 151, 240) (see Table 1). In the first year Norplant is about as effective as the first year of progestin-only injectables, vasectomy, or tubal ligation (154).

Pregnancy rates among Norplant users have been higher among heavier women than among lighter women. In pooled data from Population Council studies, women weighing 70 kg or more had a cumulative pregnancy rate of 7.6 per 100 over five years of use compared with 0.2 per 100 for women who weighed 50 kg or less (151, 219). During the first two years of Norplant use, pregnancy rates were similar for women of different weights, but the pregnancy rate increased for heavier women after the second year as the daily release of levonorgestrel diminished (219). It is not known whether the differences in pregnancy rates are due to dosage requirements, genetic factors, metabolic characteristics due to different diets, or other causes (10).

Preliminary data suggest that pregnancy rates may be lower in all women and may differ less by weight with new tubing that has been introduced by the manufacturer, Leiras Oy (219, 224). By the end of 1992 the Finnish company will produce Norplant implants only with the new tubing.

If a woman wants to continue using Norplant longer than five years, she can have the original capsules removed and a new set inserted. After five years of use the capsules continue to release levonorgestrel but in gradually decreasing amounts; thus the risk of pregnancy increases. All women should have the capsules removed after five years in any case because little is known about the effects of implants left in place longer.

Reversible. The implants may be removed at any time. Within 96 hours there is little progestin left in the blood (45). Thus a woman's previous level of fertility returns quickly. In a study of 17 Nigerian women who discontinued Norplant, 14 ovulated within four weeks, and all ovulated within seven weeks. Also, cervical mucus gradually increased, and by the seventh week 80% of the women had mucus levels sufficient to facilitate pregnancy (110).

Several small studies show that more than 75% of women who want to become pregnant do so within one year after the implants are removed, a rate similar to those for most other methods (57, 140, 151, 191, 209, 219, 232). In studies of 260 women of similar age and parity in Indonesia and Chile, pregnancy rates at four months were similar to those of women who had stopped using the IUD and higher than those of women who had stopped using injectable contraceptives, which are known to delay the average return of fertility somewhat beyond when the next injection would have been given (8, 57). The length of time that a woman has used Norplant does not affect how soon she conceives after the capsules are removed (57, 232). In the Nigerian study, however, those with regular cycles while using Norplant had more cervical mucus; they also ovulated and became pregnant more quickly after discontinuation (110).

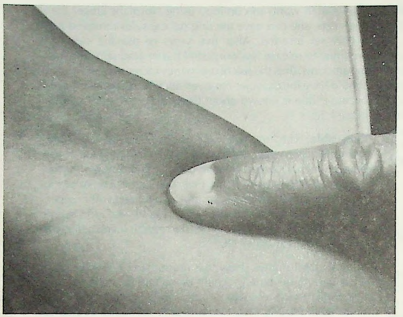
Continuation Rates

Continuation rates for Norplant in clinical trials have matched or exceeded rates in clinical trials of the IUD, the other multi-year reversible contraceptive method (3, 126). The average user in clinical trials has relied on Norplant for about 3.5 years (224). Rates have varied, however. In five studies around the world, 76% to 90% of users completed one year of use, and 33% to 78% completed five years (219, 224). Most women who discontinue Norplant for method-related reasons cite the changes in menstrual bleeding patterns that are common with this method. Others have the capsules removed because of headaches, weight gain or loss, hypertension, expulsion of a capsule, acne, hair loss, or hair growth. Norplant users in clinical trials had the capsules removed for other reasons as well. Some wanted to become pregnant, or their husbands objected to implant use. Others were moving, or they were widowed or divorced (7, 14, 107, 187, 190, 219, 230).

Side Effects

The side effects of Norplant resemble those of progestin-only pills (minipills) and progestin-only injectables. Change in bleeding patterns is by far the most common side effect.

Bleeding patterns. In various clinical trials 60% to 100% of women experienced menstrual changes (190, 219, 225). The changes that women experience vary greatly. They include bleeding on more days per cycle, heavier bleeding, spotting between periods, infrequent or scanty bleeding, and amenorrhea (no bleeding at all).



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A thin woman may see the outline of the capsules when she extends her arm. Most women can feel the capsules with their fingers, but they cannot see them. Some women are pleased when others notice their implants.

Women who weigh less may be more likely to experience amenorrhea. For example, in a study of women in the US who weighed an average of 65 kg, 7% were amenorrheic (201). In contrast, 20% to 30% of women were amenorrheic in a study in Sri Lanka and the Philippines, where women are generally lighter (21). In a study of 1,000 Norplant users, lighter women in Chile, Sri Lanka, and Thailand had less irregular bleeding and less intermenstrual bleeding than heavier women, but the pattern was reversed among Chinese women, suggesting that dietary, genetic, or other factors may influence bleeding patterns (10). It is impossible to predict accurately, however, just what pattern an individual woman will experience.

A Norplant user who has regular menstrual periods may be ovulating regularly and therefore face greater risk of pregnancy (54, 58, 201). In a US study of Norplant use, the cumulative 5-year pregnancy rate was 1.4 per 100 women overall but 17.4 per 100 for women with regular bleeding patterns (201). Women in the US study were heavier than those in other clinical trials, and heavier women are more likely to ovulate (47). The women in the study were not using implants made with the new tubing, which is expected to lower pregnancy rates.

Although a woman may experience bleeding at shorter intervals or bleeding on more days, she is likely to lose less blood than if she had a normal menstrual period (219). In some studies the hemoglobin levels of Norplant users are higher than those of control groups—a beneficial effect for anemic women (64, 73, 151, 201, 219). Not surprisingly, women whose bleeding decreased while using Norplant were most likely to have higher hemoglobin levels (73).

Other physical effects. Clinical trials comparing Norplant and IUD users find that certain conditions are statistically associated with Norplant (see Table 2). These conditions include headache, nervousness, nausea, dizziness, dermatitis (skin rash), acne, change of appetite, hair loss, increase in facial or body hair, breast tenderness, nausea, and enlarged ovarian follicles (14, 51, 107, 151, 174, 190, 219). Although women who used Norplant reported these conditions more often than did women who used IUDs, it is not clear how implants might cause them. Acne, hair growth, and hair loss may be due to the androgenic activity of the hormone and are seen in women using oral contraceptives that contain levonorgestrel (26, 51). Ovarian follicles sometimes become large enough to feel like cysts to a physician doing a pelvic examination. These follicles usually disappear without treatment. Surgery is necessary only on the rare occasions that the follicles twist and rupture, causing pain (174).

Insertion-site complications. If aseptic technique is used during insertion, the implant site seldom becomes infected. Other insertion-site complications also are uncommon. A pooled analysis involving 2,674 first-year users in seven countries found that 0.8% experienced infection, 0.4% experienced expulsion of a capsule, and 4.7% had temporarily irritated skin at the insertion site (104).

Insertion-site complications did not always occur immediately after implantation. Some 35% of infections and 64% of expulsions took place after the first two months of use. Similarly, 36% of skin irritations occurred after 4.5 months or more of use (104).

Some clinics have lower rates of infection at the insertion site than others. The differences suggest that some providers are more careful than others about maintaining aseptic conditions during insertion (24, 78, 104, 105).

Duration of side effects. Side effects, including disruption of bleeding patterns, appear to be most common and most severe during the first year of use, when progestin levels in the blood are highest (186). In one study 72% of participants had irregular bleeding patterns during the first year, but by the fifth year only 38% had irregular bleeding patterns (201) (see Figure 1). Women who abandon Norplant

Table 2
Norplant Side Effects
*Conditions Other than Changes in Bleeding that Occurred Significantly More Often with Norplant than with IUDs in Two Multinational Studies**

	% Developing Condition in First Year of Use			
	Study 1		Study 2	
	Norplant	IUD	Norplant	IUD
Headache	16.7	7.0	18.5	10.2
Ovarian enlargement	11.6	2.0	3.1	2.6
Dizziness	8.1	4.0	5.6	5.9
Breast tenderness	6.8	1.7	6.2	4.7
Nervousness	6.8	2.0	6.2	2.4
Nausea	5.1	1.7	7.7	4.0
Acne	4.5	1.0	7.2	2.6
Dermatitis	3.8	0.7	8.2	1.9
Breast discharge	3.5	2.7	5.1	1.9
Change in appetite	3.5	0.7	6.2	1.9
Weight gain	3.3	1.0	6.2	0.9
Hair growth or loss	1.8	0.5	2.6	0.5

**Condition occurred more frequently with Norplant in at least one study or in combined results.*
Source: Population Council (159)

Next Generation of Implants Tested

The progress of Norplant implants has set the stage for the development of other implants. Several different hormonal implants now under development may follow Norplant. All involve fewer capsules than Norplant, and some are biodegradable—that is, they dissolve harmlessly in the body and do not require removal.

Norplant II

The first implant to follow Norplant is likely to be Norplant II. The Population Council is developing this implant, which consists of two rods slightly longer than Norplant capsules. While each Norplant capsule contains levonorgestrel in a cavity, the Norplant II rods contain levonorgestrel embedded homogeneously within a Silastic rod, which is covered by a thin sheath of plain Silastic (155, 175). Side effects are similar in type and frequency to those of Norplant (142, 204, 207), but Norplant II should be easier to implant and to remove because there are fewer rods. Clinical tests on an early version indicate that it is effective for at least three years (38, 106, 151, 162, 180, 206, 219, 232). The new formulation of Norplant II now being tested, however, may prove to be effective for up to five years (183). Clinical studies now in progress will be used to support applications for regulatory approvals, which may be filed by the mid-1990s (249).

Implanon

Implanon, developed by Organon International, is a single 30 mm Silastic rod that releases the progestin 3-keto desogestrel at the rate of 30 µg per day. Like Norplant, Implanon can be placed under the skin with a trocar. Implanon appears to be effective for two to three years. Removal is quick and relatively simple since there is only one rod to locate. Bleeding patterns are similar to those seen with Norplant, but 3-keto desogestrel may inhibit ovulation more often than does levonorgestrel at the levels released (112, 141). Clinical trials of Implanon are underway in the US, several European countries, and countries in East Asia including Indonesia. Depending on the results, Organon will decide whether to apply for regulatory approval in the US and elsewhere. Organon also is attempting to develop a biodegradable version of Implanon but has not yet begun trials (112).

ST-1435 Single-Rod Implant

The Population Council is now testing a single modified Silastic implant using the new progestin ST-1435, which has a contraceptive effect and side effects similar to those of levonorgestrel. The implant, effective for two years, contains ST-1435 crystals encased in a rate-limiting cellulose membrane in the Silastic capsule, which releases the progestin at the rate of 100 µg per day. Like other effective progestins, ST-1435 both inhibits ovulation and thickens cervical mucus to prevent pregnancy. Unlike most other progestins, however, ST-1435 appears to have no effect on blood cholesterol levels. Also, it is inactive when swallowed and so would have no possible effect on a nursing infant. The Population Council has completed early clinical trials on 120 women in Chile, the Dominican Republic, and Finland; has plans for multicenter trials; and expects this implant to be on the market by the year 2000 (84, 183, 237).

Capronor

The Research Triangle Institute currently is developing two new versions of its biodegradable implant Capronor—Capronor 2 and Capronor 3. Capronor 2 is a 4 cm capsule of the polymer caprolactone filled with 18 mg of levonorgestrel. Recent research shows that two capsules may be required with this formulation. Capronor 3 is a single 4 cm co-polymer capsule (a caprolactone and trimethylenecarbonate blend) filled with 32 mg of levonorgestrel. Thus far, no human trials have been conducted with these new formulations, but nonhuman primate studies are encouraging and indicate very steady release rates in both versions. The co-polymer blend releases the drug more readily, allowing a thicker capsule that produces a more steady release of the hormone. The co-polymer also biodegrades more quickly than the single polymer (30).

In earlier formulations of Capronor—which consisted of levonorgestrel suspended in an oily solution of ethyl oleate within caprolactone tubing—clinical studies on women showed promising results for a biodegradable implant. It was effective for only 8 to 10 months, however, in part because of an unsteady release rate caused by the ethyl oleate vehicle, now eliminated.

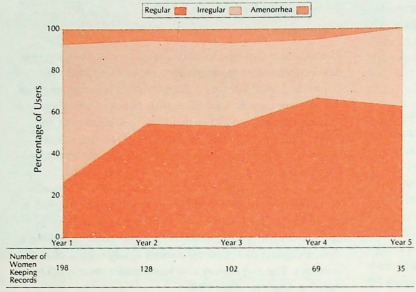
The Capronor tubing appears to be easier to insert and remove than Norplant's Silastic tubes in part because the caprolactone polymer has a slipperier surface and offers less resistance in body tissues (52, 128). The capsule remains intact through the 12-month period of levonorgestrel release. Thus it may be removed during this interval if desired. Later, however, over several years the capsule biodegrades gradually to E-hydroxycaproic acid, then to carbon dioxide and water, which are absorbed by the body (50). Capronor may be available by the end of the 1990s.

Norethindrone Pellets

Small pellets made of 90% norethindrone (NET) and 10% pure cholesterol are another biodegradable implant, now under study by Family Health International. The very small amount of cholesterol in each pellet—less than 2% of the cholesterol in a single chicken egg—helps the pellets maintain integrity and is considered harmless. Current clinical studies in the US are testing regimens of four and five pellets. Each pellet is 8 mm long and contains about 35 mg NET. The hormone is released as the pellets gradually biodegrade over a 12-month period and then disappear completely within 24 months. During the first 12 months—the period of contraceptive effectiveness—the pellets can be removed if desired. The pellets are inexpensive to make. It may be many years before the pellets become available; researchers are still testing different formulations in an attempt to improve efficacy (77, 119, 128, 211).

Figure 1. Bleeding Patterns

Based on the Dominant Pattern of Bleeding Reported for Each Year of Implant Use During Five Years of Use, 198 Women, United States



Source: Shoupe et al. (201)

because of bleeding problems account for part of this decrease, but some women who continue to use Norplant experience decreases in bleeding over time. In a study of 116 women who kept menstrual diaries for five years, the number of bleeding and spotting days decreased each year from a mean of 92 in the first year to 70 in the fifth year (151, 219). In some women a bleeding pattern becomes established by six to nine months, but that pattern may not be a monthly cycle. The pattern may change little thereafter (24, 122, 219, 247).

One small study suggests that normal menstrual patterns resume after Norplant use. Of 12 Singapore women who discontinued use because of changed menstrual patterns, all reported normal periods one year after removal (209). The World Health Organization (WHO), Family Health International (FHI), and the Population Council are now conducting a postmarketing study on reversal of side effects after discontinuation as well as other aspects of Norplant use.

Ectopic pregnancy. As with other hormonal contraceptive methods, ectopic pregnancies among Norplant users are a concern in the rare event that conception takes place. Progestin may reduce the motility of the fallopian tubes, slowing the progress of a fertilized egg and increasing the chances of implantation in the tube rather than the uterus (201). Ectopic pregnancies can rupture tubes and cause internal bleeding and death.

Among Norplant users the rate of ectopic pregnancy is lower than among women who use no contraceptive method. In the US the estimated ectopic pregnancy rate among women who do not use contraception is 6.5 per 1,000 woman-years. The rate may differ substantially in other countries (121, 214). Among Norplant users in clinical trials, the rate of ectopic pregnancies was 1.3 per 1,000 woman-years (151). By comparison, the estimated ectopic pregnancy rate for unmedicated IUDs is about 1.2 per 1,000 woman-years of use, and the estimated rate for combined oral contraceptives, which prevent ovulation, is 0.4 per 1,000 woman-years (214). The rate of ectopic pregnancies is low for Norplant users because there are so few pregnancies at all. A higher percentage of the pregnancies that do occur are ectopic, however. In five years of clinical trials, 8 of the 46 pregnancies that occurred, or 17%, were ectopic (219, 224).

Ectopic pregnancy rates among Norplant users may be higher among heavier women and may increase with longer use of Norplant (151, 174). Health care providers should consider ectopic pregnancy when examining a Norplant user who becomes pregnant or has lower abdominal pain. The possibility of increased ectopic pregnancies with longer use reinforces the need to remove the implants after five years, at least until longer use is studied further.

Physiological Effects

Studies of physiological effects indicate that Norplant is safe. Studies have found no significant changes in liver, kidney, adrenal, or thyroid function in Norplant users (151). Studies of cholesterol levels have yielded ambiguous results (87, 151). Although levels of total cholesterol consistently decreased, half of the studies found that the level of high-density lipoproteins (HDL) significantly increased—a beneficial effect—and the other half found that HDL decreased (87, 151, 195, 202, 203, 208). The results of studies on clotting factors also vary, suggesting that other influences, such as diet, may be involved (151, 195, 205). Until more is known, the Population Council suggests assuming that clotting factors change as they do in women who use combined estrogen-progestin oral contraceptives. They do not recommend Norplant for women with blood clots in the legs or eyes, which may be evidence of active cardiovascular disease (151). Such women are at greater risk for complications in pregnancy, however. If they cannot or will not use a reliable nonhormonal method, progestin-only methods such as Norplant are preferable to combined oral contraceptives.

Norplant probably does not heighten the risk of strokes and heart attacks, as has been alleged with oral contraceptives and blamed largely on the estrogen component. Norplant contains no estrogen. Still, lacking long-term epidemiologic studies on circulatory system disease and Norplant use, which are feasible only after a method is widely used, the United States Food and Drug Administration (US FDA) and the Population Council have chosen a conservative approach and suggest that women who have hypertension, an important risk factor for stroke, should use a nonhormonal method unless their blood pressure can be regularly monitored (174). A study of 600 Norplant users in Indonesia found no change in blood pressure during the first year of use, however (123). A recent Nigerian study of 117 low-dose pill users and 76 Norplant users found that increases and decreases in blood pressure occurred with about equal frequency and in both groups. The change in either direction was moderate, but the range with Norplant was narrower than with oral contraceptives (65).

Recent studies report that glucose and insulin levels rise slightly when women start Norplant but remain within the normal range. These studies suggest that Norplant may affect carbohydrate metabolism (108, 109, 203, 205, 210, 241). A woman with diabetes can use Norplant, however, if she or a health care provider can monitor her condition.

Norplant Comes of Age

The Population Council began work on an implantable contraceptive in 1966. In the 1990s that work is reaching its objective as Norplant, the first implantable contraceptive, wins government approvals around the world and attracts more users. Over the years of development, research focused first on effectiveness and safety and then on Norplant users' opinions, the management of side effects, and program managers' needs. The Population Council has planned the introduction of Norplant to ensure that programs offer the implants with good medical care and counseling that helps women make a free and informed choice among methods.

Several organizations have cooperated in the development of Norplant. The Population Council has developed the implant concept, has conducted and overseen research and development, and is guiding the process of introduction. Wyeth-Ayerst Pharmaceutical Company carried out the toxicology studies on its drug, levonorgestrel, and Leiras Oy designed the equipment used to manufacture the capsules. The United States Agency for International Development (US AID), the International Planned Parenthood Federation (IPPF), the United Nations Population Fund (UNFPA), and governments and private organizations in several countries supported clinical and pre-introduction trials.

As of mid-1992 Norplant has been used in 51 countries and is widely available or rapidly becoming available in 14 (see table on back of "Norplant at a Glance," published with this issue). Norplant is playing different roles in the family planning programs of different countries—roles influenced primarily by the range of other methods available and differing abilities to pay for supplies and services.

History of Development

The development of oral hormonal contraception—the pill—in the 1950s paved the way for implantable methods. First with the combined estrogen-progestin pills and then with the progestin-only pills, researchers learned the dosages of these synthetic steroids required to prevent conception (191). Of all the progestins, or progesterone-like compounds, tested, levonorgestrel eventually became one of the most widely used in oral contraceptives as well as the progestin chosen for Norplant (93).

The method of delivery, not the active agent, makes Norplant unique among contraceptives. Silastic, a polymerized silicone rubber material, is used in surgical tubing, pacemakers, and prosthetic devices because it is well tolerated by the body. (Unlike the silicone gel in the now-controversial breast implants used for prosthetic and cosmetic purposes (246), Silastic is a solid and does not leach into body tissue or circulation.)

In 1965 Sheldon Segal, then head of the Population Council's biomedical research staff, happened to discuss the properties of Silastic over lunch with a representative of its manufacturer. The conversation concerned an experiment in which a dye from Silastic tubing used in canine pacemakers dispersed and harmlessly disappeared into the animals' systems (93). This discussion suggested to Segal that a similar slow diffusion of progestin might provide long-term contraception—a conclusion soon confirmed by research (192).

Horacio Croxatto, a Chilean physician then a Fellow at the Population Council, developed the delivery system by creating the capsule (93). Over time his research team tested various synthetic steroids and various capsules in animals to ascertain their different release rates.

Clinical trials. Multinational blind comparative studies took place in 1974. Researchers tested implants containing eight different progestins in 36 different doses with 1,100 volunteers (93). These studies gathered information on efficacy, duration of effect, and side effects.

Clinical trials of the three most promising capsule and progestin combinations began in Brazil, Chile, Denmark, the Dominican Republic, Finland, and Jamaica in 1975 (93). In these trials 1,500 women volunteered to use the implant formulations, which were randomly assigned. The volunteers were asked to keep records of their menstrual patterns and to return for follow-up visits for one year (93, 151). In 1977 levonorgestrel was chosen as the progestin for the new implants because of its long period of effectiveness and high level of effectiveness, and because extensive toxicity test results were already available (93, 151). More clinical trials began between 1980 and 1982 in Chile, the Dominican Republic, Finland, Sweden, and the US (151).

Pre-introduction trials. Norplant pre-introduction trials began in 1980 and have taken place in 43 countries in all regions (see table on back of "Norplant at a Glance"). Pre-introduction trials typically involve more women and more service sites than clinical trials. About 40,000 women have participated, although published results are not available for most of these studies. These trials help to design appropriate training and informational materials for providers and users, to acquaint local medical personnel with the method, and to gather country-specific information for local regulatory approval. In addition, this experience with a small program assists managers later with logistics, training, and service delivery on a larger scale (19, 233). The Population Council has collaborated with FHI, the Program for Appropriate Technology in Health (PATH), and

Chronology of Norplant Development

- **1966** Research on implants begins
- **1967** First tolerance trial
- **1974** First clinical trial, in Chile
- **1975** Clinical trials in 6 countries; pharmacological studies in US
- **1977** Levenorgesterel formulation chosen
- **1979** NORPLANT registered as trademark for implants
- **1980-82** Pre-introduction trials in 5 countries; clinical trials in 5 more countries
- **1983** Leiras Oy is licensed to produce Norplant; Finland is first to give regulatory approval
- **1984** Pre-introduction trials begin in11 more countries
- **1985** WHO and IPPF review Norplant favorably; Sweden approves Norplant
- **1986** IPPF makes Norplant available; Dominican Republic, Ecuador, Indonesia, and Thailand approve Norplant
- **1987** China, Colombia, Peru, and Venezuela approve Norplant; Pre-introduction trials in 12 more countries
- **1988** Application made to US FDA; Chile and Sri Lanka approve Norplant
- **1990** US FDA approves Norplant
- **1991** 1.6 million women in 51 countries have used Norplant; 23 countries have given regulatory approval
- **1992** Leiras Oy switches to soft tubing, semi-automatic production

Orange type = Early implant research before current Norplant formulation was determined

Sources: Adapted from Population Council (151, 171), IDRC/Population Council (93)

the Association for Voluntary Surgical Contraception (AVSC) in pre-introduction and information efforts.

WHO, FHI, and the Population Council now are collaborating on a postmarketing study of 8,000 Norplant users and 8,000 sterilization or IUD users in Barbados, Chile, China, Colombia, Indonesia, Sri Lanka, and Thailand. Focused on safety, the study will follow up all of the women as they use their contraceptive method for five years. All women who discontinue any time after six months of use also will be followed up. The findings should be able to identify health-related events associated with implant use that occur with a frequency of one per 2,000 women or greater (158, 224).

Regulatory Approvals

By August 1992 Norplant had been approved for marketing in 23 countries and adopted by family planning programs in 3 more countries that have no regulatory approval process. The first country to approve Norplant was Finland, in 1983. This approval permitted Leiras Oy to export the capsules. As manufacturer of Norplant, Leiras Oy prepares the documents for submission to national drug regulatory agencies in all countries except the US. The Population Council, which applied to the US FDA, received regulatory approval for Norplant on December 10, 1990. Most countries require regulatory approval before a drug can be marketed, but manufacturers do not always immediately market the approved product. Thus Norplant is not widely available in all countries where it has been approved.

Leiras Oy and Wyeth-Ayerst Pharmaceutical Company have agreed on Norplant production and distribution. Wyeth-Ayerst produces levonorgestrel and sells it to Leiras Oy. Leiras Oy manufactures all of the implants and sells them to Wyeth-Ayerst, donor agencies, government family planning programs, and pharmaceutical distributors in countries other than the US and Canada. Wyeth-Ayerst markets Norplant in the US and, when approved, in Canada.

As noted (see p. 5), Leiras Oy has changed the Silastic used in making the capsules. This shift required changing the manufacturing equipment used in semi-automated production. Some regulatory bodies including the US FDA had earlier approved the capsules made manually with the new tubing. Leiras Oy must submit a supplement to the approved US FDA application to cover implants produced by the semi-automated process. Most other countries have already certified the implants with the new tubing made by the semi-automated manufacturing process. Supply of Norplant has not been affected by these changes (86, 257).

Norplant in the United States and Europe

Early clinical trials in the US, supported by US AID, involved 400 women and took place in the 1980s in Los Angeles, San Francisco, and New Brunswick, New Jersey (224). Wyeth-Ayerst began preparing for nationwide introduction in 1988, when the company decided to market Norplant in the US (175). In the first two years that Norplant was available in the US, about 500,000 women obtained implants. Almost three-quarters were under age 30. About half were married (264).

While the price for implants is US$23 per set for donor agencies and developing-country, not-for-profit family planning programs (see p. 15), in the US the price for a set of Norplant implants is US$350 to both public clinics and private physicians (117, 252). All contraceptives are more expensive in the US than in developing countries. The US price covers Wyeth's expenses for its training program, promotion and sales of the method, and individual packaging of each implant with all the material required for insertion. Clients pay additional fees for counseling, insertion, removal, and follow-up visits. For example, in Baltimore clinics of the Planned Parenthood Federation charge a total of about $600—$350 for the implants plus $25 for a counseling session, $45 for a physical examination, and $175 for insertion and two follow-up visits (23, 146). Removal at Planned Parenthood clinics in Baltimore costs the client about $100. Others' fees vary, but total cost can be as high as $1,000 (70). Despite the costs, some providers in the US have a waiting list for implants because demand exceeds supply (15, 82).

Many US women have health insurance that will pay for Norplant. As of August 1992, 46 of the 58 major health maintenance organizations in the US had decided to reimburse women for at least part of the cost of Norplant insertion (257). Health maintenance organizations provide all health care to members who pay a periodic fee. Private insurance organizations, such as Blue Cross, also will reimburse in some cases (15, 260). Medicaid, the government-funded health insurance program for the poor, pays for the implants and a portion of the cost of associated medical services. Some public clinics that provide free or reduced-price services doubt that they will offer Norplant, however. They can serve more clients when they buy less expensive methods (251, 252). Physicians and nurse-practitioners at clinics can apply for free implants to the new Norplant Foundation established by Wyeth-Ayerst to help low-income women. The foundation has an initial US$2.8 million to provide implants to about 10,000 US women who cannot afford the method and do not qualify for Medicaid (11, 69, 117, 250). The foundation does not pay service costs. It has recently changed its requirements so that providers no longer must fill out a form for each woman who wants Norplant (68).

In Europe the first countries to approve Norplant were Finland in 1983 and Sweden in 1985. In both countries many contraceptive methods are available. In Finland about 3% of women who use contraceptives currently use Norplant (248). About 70% of the 20,000 Finnish women who use Norplant received their implants in private clinics, and the rest received their implants in government family planning centers. On average, Norplant insertion costs US$200 to $250. The government has subsidized 60% of these costs in public clinics, but the amount of the subsidy is decreasing (248).

Elsewhere in Europe, Leiras Oy has guided clinical trials in Belgium, Bulgaria, Denmark, France, and Germany. Norplant has been approved in Czechoslovakia and the former USSR, but it is not widely distributed in these areas (118, 248).

Norplant in Three Countries

Indonesia, Thailand, and Colombia are among the first countries where Norplant is widely available. Patterns of use in these countries vary, reflecting differing circumstances.

Indonesia: Widespread Norplant Use

Over one million women in Indonesia have received Norplant through the extensive government family planning program. Indonesia aims to reach zero population growth by 2035–2050 (92). Achieving this goal requires substantial increases in the number of contraceptive users (127). At present, 49% of married women use a modern method of

contraception. The government family planning program hopes that introducing new methods such as Norplant will attract new clients to family planning (91, 92). Norplant is a valuable new method in the Indonesian program, particularly because sterilization is not available through the government family planning program. After clinical trials in 1981, the national family planning coordinating board, Badan Koordinasi Keluarga Berentjana Nasional (BKKBN), planned to offer Norplant primarily to women in remote areas where resupply of pills, condoms, or other contraceptives was difficult (123). That same year, however, the Board of Islamic Religious Leaders issued a statement opposing all forms of sterilization (5). As a result, government facilities stopped offering voluntary sterilization as part of the official family planning program (18, 127). By that time BKKBN had begun a campaign to encourage couples to use more effective, long-term methods in place of oral contraceptives and condoms. Therefore they urged women who wanted to delay or end childbearing to use Norplant or IUDs (127). Islamic leaders have recently stated that sterilization may be used judiciously, but it is not widely available (40).

A provider in Indonesia shows a couple where Norplant implants are placed. More than one million Indonesian women have used Norplant.

In 1984 BKKBN, with support from UNFPA, bought 30,000 implant sets and made Norplant available at 87 hospitals and large health centers (97, 247). UNFPA supplied another 25,000 sets in 1987 and 109,000 sets in 1988 (243). The Indonesian government also has purchased implant sets with its own funds and with loans from the Asian Development Bank and, since 1990, the World Bank (175, 234).

Since regulatory approval in 1986, the number of new Norplant users has grown each year (92). Norplant now accounts for 3% of Indonesian contraceptive use (91). Most Norplant users live in the densely populated areas of rural Java, where providers were first trained. BKKBN has introduced the method in other areas with less dense populations, and 6% to 7% of contraceptive users in some of these areas use Norplant (91).

A variety of Indonesian women like Norplant. In rural Java, where the method was first widely used, most women are Muslim and do not accept sterilization or the pelvic procedure necessary for an IUD (5). But women in other areas also like implants. In a national survey of 3,000 users conducted by BKKBN, 72% of the women interviewed said that they would recommend implants to others. About 65% of users did not want more children, but 30% definitely desired a future pregnancy (90).

By 1991 Norplant was used in all Indonesian provinces, especially in rural areas (91). Government programs served 95% of Norplant users—50% at health clinics, 21% at temporary service sites called "safari," 16% through health posts or field workers, and 7% at hospitals. Private practitioners served 4% (91). Two-thirds of married women knew about implants, and 60% knew where to obtain them (91).

BKKBN has set a national goal of 300,000 new Norplant users per year (92). As with goals set for other methods, provincial program managers must decide what portion of the national goal they can meet. Each year they assess past use of Norplant and other methods, estimate the anticipated number of new users, and then request supplies and service support accordingly (100). Hospitals, clinics, and other centers receive their supplies and their funding according to their expected number of clients. At current international prices, it would cost more than US$8 million each year to supply Norplant capsules for the intended 300,000 new users, most of whom will use public clinics. Indonesia is considering local manufacture in hopes of reducing costs (92, 98).

Indonesian officials are now reassessing their past emphasis on numbers of new users. Health officials have concluded that, although initial acceptance of family planning has been high, continuation rates need to be higher. Therefore family planning services in Indonesia are now emphasizing high-quality service, including better counseling and screening, as well as numbers of new users. Temporary service sites—"safari"—are no longer used to provide implants because program managers found it difficult to screen and counsel women adequately at such sites (92). Also, offering Norplant only in fixed facilities should hold rates of infection at the insertion site to a minimum and improve record-keeping.

Some 27 regional centers now train physicians to provide Norplant, including insertion and removal. Midwives also are trained to insert Norplant under the supervision of a trained physician, but they may not remove Norplant (34). In addition, the general family planning curricula in medical and nursing schools cover the implant method. Recently, Indonesia has begun training more physicians in removal techniques because need for removals is growing.

Currently, women who receive Norplant in a public clinic pay nothing, while those who obtain Norplant through a private provider pay Rp. 70,000 (US$36) (41). Indonesia's Blue Circle campaign, which provides participating private physicians and trained midwives with supplies at low cost, will soon offer Norplant.

Because Indonesia has the first large implant program, it is the site of several studies exploring long-term side effects, women's attitudes towards implants, and the planning requirements for a high-quality program. Indonesia is one of the locations in the multinational postmarketing study. BKKBN also is conducting its own internal evaluations of Norplant program needs (92). Operations research studies are currently underway to review use dynamics, follow-up, and provision of removal services for women who have used their implants for five years (175). The program also is participating in preliminary field trials of other contraceptive implants such as Implanon (see box, p. 7) (92).

What Women Say About Norplant

Most users like Norplant, and a majority would recommend it, according to survey and focus-group responses. Research on users' attitudes was part of some pre-introduction trials.

Most Users Recommend Norplant

More than 75% of Norplant users would recommend implants to their friends, according to research in Brazil, Egypt, Indonesia, Nigeria, the Philippines, Sri Lanka, and the US (16, 21, 22, 51, 62, 63, 79, 90). As one Norplant user commented, "For me this method is the best....To me, the absolute certainty that you are not going to become pregnant is something that you cannot buy with anything" (178).

Best-Liked Features

Most Norplant users found that they liked its effectiveness, long duration of effectiveness, and reversibility (24, 51, 62, 102, 190, 230, 262). They also liked the convenience of few clinic visits: no resupply, as with condoms or pills, and nothing to remember at the time of intercourse (79).

Concerns About Bleeding Changes

Most women experienced changes in menstrual patterns, but they reacted differently (24, 51, 79). In one US clinical trial 79% of participants reported menstrual changes, but only 18% were bothered by them (136). In contrast, frequent bleeding bothered some Muslim women, whose religion forbids them to pray or to have sexual intercourse while menstruating (262). Some other women also said that frequent bleeding interfered with sexual relations.

Some women were bothered by amenorrhea and did not understand that missing menstrual periods while using Norplant is not harmful. Several women in the Dominican Republic, for example, felt that the "bad blood" was not draining from their bodies (179). One woman's remark points out the value of thorough counseling about menstrual changes: "Older people in my family tell me it's absolutely necessary to have your period. If not, one can have problems. But the doctor says there's no problem" (178).

Feelings About Other Side Effects

Women's attitudes about other side effects also varied. Headache, depression, and hair loss—conditions that some women attributed to Norplant—troubled most who experienced them. Weight gain, however, was a positive effect in the Dominican Republic, Egypt, and Indonesia but a negative one in the US (51, 262). Weight loss was unacceptable in the Dominican Republic, Egypt, Indonesia, and Thailand. Implants usually cannot be seen under the skin, but in any case most women were not concerned about other people seeing their implants (102, 190). Indeed, some women in the US and the Dominican Republic were proud when people noticed their implants (136, 261).

Attitudes Toward Insertion and Removal

Most women in Egypt, the Dominican Republic, Indonesia, Thailand, and the US said that they felt no pain at the time of insertion (51, 62, 190, 262). Removals were not painful for most women, either, although removal generally took longer and was less comfortable than insertion.

Some women in Bangladesh, Egypt, the Dominican Republic, Indonesia, and Thailand reported that health workers were reluctant to remove the implants (101, 126, 253, 262). Some other women did not know that implants had to be removed after five years or that they could be removed earlier. Still others thought that the removal procedure involved major surgery or was done without anesthesia (262). Providers must be thoroughly trained and supervised to ensure that they give full and accurate information and do not refuse requests for removal.

The Influence of Husbands

Husbands influenced women's decisions about Norplant. Almost all of the women in the Dominican Republic, Egypt, Indonesia, and Thailand discussed their decisions with their husbands before choosing implants (29, 262). In Bangladesh, Haiti, Nepal, and Nigeria, one-third of women who decided not to use Norplant mentioned their husbands' disapproval as a reason (102).

Some users' husbands became uneasy about side effects. Some were alarmed by their wives' frequent bleeding, and some women mentioned this as a reason for removal (190, 262). Some husbands in the Dominican Republic, Egypt, and Nepal were concerned that amenorrhea was not healthy (102, 262). In Thailand 5% of women questioned said that their husbands disliked the menstrual irregularities or distrusted a method that they considered experimental (190).

The support of family and friends was often crucial to Norplant users' ability to adjust to the method. A participant in a Norplant study said, "Both my husband and mother know that I am using Norplant. In fact, it is my mother who keeps track of my clinic appointments" (178).

Women's Suggestions for Better Services

In focus-group discussions women made detailed comments about the health services they had received, and they suggested improvements. Women in the Dominican Republic and Indonesia wanted more counseling before insertion and during the first six months of use (90, 262). Women in Egypt did not want follow-up examinations, particularly if the health clinic did not have a female physician. In contrast, women in the Dominican Republic approved of the frequent medical check-ups that they received as part of pre-introduction trials (262). Some women suggested informational videos in waiting rooms as well as written material. Others were frightened by photographs, intended to train physicians, that were hung in the waiting room (262). Some women have suggested that providers show women the capsules during counseling.

Women wanted to learn not just for themselves but also to tell others. A Dominican woman objected when the provider told her to look away during her insertion procedure. She said, "I think the doctor should let one see the process if one wants to. People always ask how that is done, and how the implants are put in your arm. If you're not allowed to see, how can you explain to people who ask?" (178).

Thailand: Limited Use of Norplant

Thai family planning managers expect Norplant to attract new users to their program. The Thai government established the National Family Planning Program (NFPP) in 1970, and the contraceptive prevalence rate grew from 15% in 1969–70 to about 71% in 1987—a level like those in developed countries (27, 114, 138). When the rate of increase in prevalence slowed in the 1980s, however, NFPP looked to Norplant and injectable contraceptives to attract women who were not using modern contraceptives.

A pre-introduction trial of Norplant began in 1980 with 1,000 volunteers (190). In 1985 NFPP took the first steps to introduce the method nationally. NFPP held an orientation meeting for the chief medical officers of all 73 provinces, won regulatory approval for Norplant in 1986, prepared informational materials for trainers and general-practice physicians, trained trainers and other physicians in insertion and removal, and obtained implants and trocars (114, 151).

In 1986, 700 physicians were trained, one from every district hospital (27). They were to serve an expected 10,000 users nationwide (114). When import duties increased the cost of the implants from the 1986 price of US$13 to $36, however, NFPP bought one-third the number of implants originally planned (139). Supplies were not adequate to meet demand throughout Thailand (27). Thus implants were offered only to women in the remote northern hill areas and to Muslim women in the south, as an alternative to sterilization (139).

Training of physicians has expanded steadily (97). Nurses in some hospitals also have learned insertion, removal, and counseling (95). Norplant is discussed in medical and nursing school curricula, and some doctors and nurses are learning insertion and removal. For the most part, practicing health care providers learn the procedures and counseling skills informally by observing experienced practitioners.

In 1991 the Thai government bought 40,000 implant sets and made Norplant part of the contraceptive services available at all district hospitals. By mid-1992, 150,000 Thai women had used Norplant (249). Because physicians have limited time available to do insertions, hospitals with nurses trained in insertion provide more Norplant than hospitals without specially trained nurses (95).

Women pay for the implants according to a sliding scale. Poor women and those in remote areas receive Norplant free of charge; other women pay something, and a few pay as much as US$8 for the implant and insertion (95, 97, 139). Occasionally, NFPP runs campaigns to promote long-term family planning methods. To attract new users, they offer Norplant, IUDs, and voluntary sterilization without charge for a limited time (76). NFPP expects Norplant to appeal to about 5% of women who seek contraceptives (139).

Thai couples have many contraceptive options, and NFPP considers Norplant appropriate only for women who want long-term birth spacing or who live in remote areas. The program discourages short-term use of Norplant because of the cost (27). Women over age 30 with several children are encouraged to choose either IUDs or voluntary sterilization rather than the more expensive implants.

Colombia: Norplant in the Private Sector

In Colombia the private sector has played the largest role in offering Norplant. The family planning association Asociación Pro-Bienestar de la Familia Colombiana (PROFAMILIA), an affiliate of the International Planned Parenthood Federation (IPPF), provides most contraceptive services, including Norplant. Some private physicians offer implants, too.

Use of Norplant has grown gradually since government approval in 1986. The Corporación Centro Regional de Población (CCRP), a private research institute, began the first pre-introduction Norplant trials at two hospitals of the Ministry of Health (18, 239, 254). In 1988 and 1989 more trials, involving nearly 3,000 women, began in PROFAMILIA clinics (97). An additional 1,000 women received implants from PROFAMILIA in 1990 through the postmarketing study. In 1991 about 15,000 women were using Norplant in Colombia, and about 15,000 more are expected to receive implants in 1992 (239).

The first Colombian physicians to offer Norplant, from the Ministry of Health and PROFAMILIA, trained in the Dominican Republic. These physicians informally trained others at PROFAMILIA until 1991. Then 2-day seminars began to train personnel in all 40 PROFAMILIA clinics,(239).

In 1987 the Sociedad Médico Farmacéutica (SOMEFA), a society of physicians in private practice, became the distributor of Norplant implants in Colombia (18). In cooperation with the CCRP and the Fundación Sante Fe (a private hospital in Bogota), SOMEFA organized training courses in insertion and removal. Since 1990 more than 50 physicians in private practice have attended these courses, and more than 500 health professionals have attended informational seminars in five locations (18). SOMEFA has distributed over 1,000 implant sets to trained private physicians and expects that each will insert five implants per month (18, 97).

PROFAMILIA currently charges US$30 for Norplant if the client is not involved in a research study. This charge covers the implants, insertion, follow-up, and removal. While the charge is below PROFAMILIA's costs, it is still expensive for many Colombian women (239). Although PROFAMILIA charges less than cost for all methods, it charges more for implants than for any other method including vasectomy and tubal ligation. Currently, PROFAMILIA is undertaking two studies on the cost of Norplant. One will study the demand for Norplant at different prices; the other will compare the cost components of Norplant and of other methods in part to determine whether Norplant is more expensive to provide than voluntary sterilization (18, 175).

Deciding on Norplant

In deciding whether to introduce Norplant, providers must assess the benefits and costs of the method. Managers of family planning programs first need to determine how this new method might meet clients' needs. They also must consider the requirements for starting and maintaining the program and how they will pay the costs. Private providers, too, must determine whether their clients will be interested in this new contraceptive method and willing to pay for it. To make such assessments, providers may want to consider:

- How will Norplant help meet women's needs?
- Will implants further program goals?
- How much will Norplant services cost?
- Can the program provide high-quality Norplant services?
- Who can help support Norplant services?

How Will Norplant Help Meet Women's Family Planning Needs?

Family planning clients are best served when they can choose from a variety of methods (35). Different clients have different needs and preferences, and any client's needs may change over the years that she uses family planning. When a variety of methods is available, clients are more likely to find a method that they like and will continue using.

In clinical trials Norplant's unique combination of features appealed to several different groups of women. Many women were attracted to Norplant because it was effective for five years but also reversible. Others liked the convenience of a method that did not require frequent clinic visits. Still others were interested in trying a new method. In clinical trial sites in Thailand and the US, 50% of new Norplant users had been using oral contraceptives before trying implants. In Thailand another 20% switched from injectables, and 12%, from IUDs

Questions Women Ask—And Answers

The following are questions that women have asked about Norplant and the answers that providers might give (51, 97, 150). Providers also may want to give more detailed information based on other sections of this report.

Q: When should I have Norplant inserted?
A: Norplant should be inserted during or soon after a menstrual period to ensure that you are not already pregnant.

Q: Can I use Norplant if I am breastfeeding?
A: You do not need to use a family planning method if you are breastfeeding without giving your child other food. If you wish to use a method, hormonal methods are not the first choice for breastfeeding women, especially for the first six weeks after birth. You may want to use another method for at least six weeks. You can use Norplant after the first six weeks of breastfeeding.

Q: Will the capsules move around in my body?
A: The capsules remain where they are placed. You should be able to feel them with your fingers.

Q: Can men use Norplant as a contraceptive?
A: Norplant is effective only for women, not for men.

Q: If the medicine is put in my arm, how can it work in my sex organs?
A: The capsules slowly release a hormone that enters the blood stream and circulates through the body. The hormone works only on the reproductive organs.

Q: If I want three years of protection, can I use three capsules instead of six?
A: Six capsules are always necessary to prevent pregnancy. Fewer capsules of this kind would not be enough no matter how long you wanted to use Norplant.

Q: Will insertion hurt?
A: Insertion is not painful. A local anesthetic is used to prevent pain in the area of the implants, and the procedure takes 8 to 10 minutes.

Q: Will my arm hurt after the insertion?
A: There may be some soreness and bruising around the implant site for a few days.

Q: Will removal hurt?
A: Removal is also done using local anesthetic, and so it is not painful. Removal does take longer than insertion.

Q: Why do I need to have the implants removed after five years?
A: The implants must be removed after five years of use until research demonstrates that they are safe longer.

Q: Can I use Norplant for more than five years?
A: Yes. After your first set of capsules is removed, you can have another set inserted, usually in the other arm.

Q: Will Norplant make me or my husband too weak to work?
A: Norplant will not weaken you or your husband. Even women who bleed more frequently do not lose more blood than they did with their normal menstrual periods. The changes in menstrual bleeding patterns do not weaken women.

Q: If my monthly bleeding stops or decreases, will bad blood build up in my body?
A: No. Many Norplant users have little or no menstrual bleeding because their bodies produce less blood. No blood builds up in the body.

Q: Will the capsules break if they are bumped?
A: The capsules are made of a soft, flexible material. They will not break if they are pressed, bumped, or touched. If you are worried that they have broken, a health care provider can check your implants. [If possible, the provider should show the client a capsule and let her handle it.]

Q: Will the implants be visible?
A: When Norplant is first inserted, there may be a bruise around the insertion site, but the bruise disappears. A small scar may form at the insertion site. Many thin women say that the implants appear as raised lines under their skin when they extend their arms. Other women cannot see them at all, but they can feel them with their fingers.

Q: Will implants protect me from AIDS?
A: No. Implants will not protect you from AIDS or any other sexually transmitted diseases such as syphilis or gonorrhea. If there is any chance that your sexual partner is infected with any sexually transmitted disease, or if you or your sexual partner has other sexual partners, he must use condoms.

Q: How long does it take for Norplant to become effective?
A: Norplant is effective within 24 hours after the capsules are inserted.

Q: How soon can I become pregnant after the implants are removed?
A: You can become pregnant within the next month. Over 30% of the women who want to become pregnant do so within three months, and 75% become pregnant within one year after the implants are removed.

Q: Can a young woman who has never been pregnant use Norplant?
A: Women who have never been pregnant, including adolescents, can use Norplant, just as they can use other hormonal contraceptives such as pills.

(107). In the US, another 14% had been using condoms, and 14% had been using diaphragms (48).

Couples dissatisfied with other methods also may choose Norplant. Women who do not want to take a daily pill may prefer the ease of implant use. So may couples who dislike using condoms, diaphragms, or spermicides at the time of intercourse. Implants also may appeal to women bothered by estrogen-related side effects of combined oral contraceptives, such as nausea and headaches, and to women who have had difficulties with IUDs.

The range of methods available will influence the appeal of Norplant. When the Indonesian family planning program decided to encourage women to use long-term methods, they offered implants, injectables, and IUDs but not voluntary sterilization (see p. 11). Because IUDs and implants do not need frequent resupply, Indonesian clinics emphasized these two methods (123). Thus in Indonesia Norplant is often a method for women who want no more children (7). Similarly, many of the women who chose Norplant in clinical trials in Egypt, the Philippines, and Sri Lanka said that they did not want more children (21, 24, 71). By comparison, in Thailand, where sterilization is widely available, women who do not want more children are encouraged to choose sterilization rather than Norplant (179, 262).

In Sri Lanka many younger women who used modern contraceptives were interested in using Norplant. As part of the Rural Family Planning Survey in 1985, interviewers told more than 2,000 women about implants and asked whether they would be interested in using them. More than one-third were interested. These women tended to be younger women who wanted to delay pregnancy for several years and who already used some form of modern contraceptive method, either alone or along with a traditional method (236).

Norplant may appeal especially to certain groups of women for geographical or cultural reasons. In Indonesia, Kenya, and Thailand, family planning program managers initially addressed Norplant services to women in remote areas where it is difficult for them to obtain oral contraceptives, condoms, and other family planning supplies (123, 153). These policies have been modified in Indonesia and Thailand, however, until it becomes possible to ensure good follow-up services for these women. Also, implants may appeal particularly to some Muslim women who may not approve of sterilization—or whose husbands or religious leaders may not approve—or who want to avoid the pelvic procedure necessary for an IUD (247, 262). These women, however, may particularly object to the irregular menstrual bleeding that can be a side effect of Norplant because they cannot pray or have sexual intercourse while bleeding.

Once Norplant is more widely used, researchers will be able to develop profiles of women who are likely to be most satisfied with implants. Then providers can use this information to advise women about contraceptive choices, and programs can use it to help design promotional and informational messages and materials (see pp. 16–17). These profiles will differ from one country to another because of religious, cultural, geographic, and programmatic factors. A study found that potential Norplant users in Bangladesh, Haiti, Nepal, and Nigeria differed in average age, education, desire for future pregnancy, and number of children. For example, in Bangladesh and Nepal the women with the least education were most interested in Norplant, but in Haiti the most educated women were most interested (102). Providers should remember, however, that some women who do not fit the profile may want to use Norplant and may be very satisfied with it. For example, young women who have no children, including unmarried women, may want to use Norplant as much as older women who have all the children they want.

Will Implants Further Program Goals?

Most family planning programs are established to improve the health of women and children and/or to contribute to socioeconomic development by slowing population growth. Thus most programs seek to increase the number of couples using family planning, increase the effectiveness of use, and lengthen the use of effective family planning methods. In the long run this is best done by making readily available the services that people want. By meeting clients' needs, Norplant can help accomplish all three goals. As a new method, Norplant can attract women who have never used an effective method and can serve women who have discontinued other methods. As a highly effective method, Norplant can improve the effectiveness of the overall method mix. As a long-acting, low-maintenance method, Norplant can extend overall continuation rates.

To what extent will Norplant attract women to contraception for the first time? At this point, evidence is slight because Norplant has not yet been widely offered in many countries. The pre-introduction trials did not promote the method to the public but instead found volunteers among women who came into family planning clinics for contraception.

There is some evidence, however, that implants may attract new contraceptive users. In Egypt, word of the new method spread, and women lined up to join the pre-introduction study (261). In Indonesia a study of 8,681 Norplant clients in 1984 found that 36% had not used any method previously (81). In Thailand 13% to 20% of women who chose Norplant in clinical trials had never used any contraceptive method before (107, 190). In a study of 550 women at 11 Thai hospitals, 12% of women who chose Norplant had never used a modern contraceptive method before. Most of the women in this last study were young, however, and just beginning to need contraceptives. Nearly all would have chosen another method if Norplant had not been available (96).

Most women who switch to Norplant from other methods will be switching to more effective contraception. For the first year of use Norplant is more effective than oral contraceptives, condoms, spermicides, and Natural Family Planning, and over five years Norplant is as effective as the most effective IUD (154).

In clinical trials Norplant continuation rates have been about the same as or better than the clinical trial rates for the IUD and better than the rates for other temporary methods (see Table 1). As with all other methods, the best way to improve continuation rates is to satisfy clients. In an Indonesian study 75% of those who were given the method that they preferred continued use for at least one year. In contrast, after one year only 15% of those who did not get the method they wanted were still using the method that they had received (144).

How Much Will Norplant Cost?

Cost is a major consideration with Norplant. The cost of the implant itself and the cost of introducing the method make implants more expensive than other methods. The implants cost nonprofit and government programs in developing

PRESENTING A NEW METHOD:

Positioning Norplant

When introducing a new family planning method, program managers can position it to attract a specific clientele—people who are most likely to find that the method satisfies their needs. "Positioning" is a marketing term that means presenting a product or service in a way that helps to distinguish it from other, similar products or services, usually by emphasizing one or a few important characteristics (1). Positioning helps to create a perception of a product or service—what marketers call an image—in the minds of both public and providers. In commercial marketing, positioning is intended to differentiate products and thus to reduce competition and encourage consumers' loyalty to a specific brand. In family planning, program managers want to position different contraceptives to help clients determine which method they want to use.

Why Positioning?

Positioning helps family planning programs assist their clients in several ways. It helps the public understand the differences among the available methods and, through the mass media, suggests reasons for choosing among methods even before people come face-to-face with providers. Thus it helps clients to make informed choices. Informed choices lead to more satisfied users and thus more effective, longer use of methods.

Positioning also helps providers, even if no special public promotion or publicity is planned initially. The positioning process anticipates how a new method will fit into a family planning program both at first and in the long run. This facilitates planning for supplies and services and informing health care providers about the method. Thus a well-planned process of positioning is important for the program and its staff. Since the positioning process involves comparison with other methods, positioning a new method such as Norplant is a good occasion to assess the positioning of other methods as well.

Positioning does not mean that only certain women will receive Norplant or that women will be denied a choice of methods. The process attempts to connect the women who are looking for certain features with the methods that have those features. All women should be able to choose the method that they prefer so long as it is medically appropriate for them and the program can provide it.

To position a product or service, marketers analyze the features of the product and the needs of the clients who might most want the product. Research

such as the pre-introduction trials of Norplant provides the basic information for this analysis. So can focus-group research and consultations with women's groups and consumer groups who speak on behalf of potential clients. The analysis may lead to a positioning statement—a slogan highlighting the product characteristics that are most responsive to the needs of intended clients. The positioning statement then becomes the starting point for message design.

Positioning Norplant: Three Examples

Characteristics of Norplant that help to position it relative to other methods include:

- Easy to use and convenient,
- Very effective,
- Reversible,
- Long-lasting,
- New method of delivery,
- Does not interrupt sexual relations, and
- Placed in the arm; a pelvic examination is desirable but not necessary (255).

After studying these characteristics, participants in a 1991 workshop convened by the Johns Hopkins University Center for Communication Programs decided to emphasize newness, convenience, and long-lasting effectiveness. Participants settled on the positioning statement: "Norplant: The new contraceptive option for women, effective up to five years" (255).

In Zimbabwe the National Family Planning Council is starting a campaign to promote Norplant along with other long-term family planning methods. Norplant pre-introduction trials are in their second year in 1992, and providers are just beginning to become familiar with the method. Physicians in government hospitals and in private practice will be the first to offer Norplant. Their clients are expected to be urban, educated people who can afford hospital or private services because their health care is paid for by employer-provided insurance. Within the past two years insurance policies have begun to cover part of the cost of family planning services. The Zimbabwe National Family Planning Council has decided to use the slogan "Norplant: The five-year contraceptive plan." One promotional poster is headlined "We have taken a five-year insurance plan." The poster is designed to attract clients who understand insurance and can afford this new method (263) (see photo, p. 16).

Similarly, in Indonesia advertisers have designed a private-sector campaign to appeal to urban professional women. These career-oriented women want to delay pregnancy for at least several years; they can afford private family planning providers; and they are attracted to new technologies. Therefore advertisements picture a career woman near her computer. The slogan used in print and on radio is "Implants from Norplant. The exclusive way of family planning" (see photo, below). Clients remember this kind of short slogan, especially when reinforced by a logo or symbol, better than a lengthy explanation. The slogan and logo cannot convey a great deal of information, but they can help to create a positive image for Norplant.

Why Care About Image?

Why deliberately try to create an image of a new product? Because any new product will soon develop an image with consumers in any case. Experience with other contraceptive methods suggests that rumors and negative news can easily overwhelm a balanced view of risks and benefits (see **Population Reports**, *Aftercontraception: Dispelling Rumors About Later Childbearing*, J-28, September-October 1984). If no organized effort is made to shape the image of the new contraceptive, happenstance or rumor will determine it. Worse yet, negative images spread by groups who oppose family planning and those who distrust new medical technologies may shape the public's perceptions.

In India rumor contributed to an inaccurate image of Norplant. Women initially heard that Norplant required surgery (39). Thus their image of Norplant was that of a major surgical procedure.

In contrast, in Indonesia and Zaire coincidence has linked the image of Norplant to traditional medicine, which sometimes involves placing small bits of gold or other material under the skin (7, 124). In fact, in Indonesia Norplant is often called by the name of the traditional implant, *susuk* (81, 173). Indonesian women may choose Norplant more readily because they are already familiar with traditional implants. This image, however, is not always positive. While some Indonesians associate *susuk* with enhanced beauty, others link it to black magic and prostitution (179).

Creating a positive image at the start saves money (145, 182). Creating a good first impression is easier and less costly than trying to overcome a bad impression once it has become established in the public mind.

Developing a positive image for Norplant or any other method is more difficult if family planning services in general have a negative image. The image of Norplant will be tied to the image of the people and organizations that provide it. No communication campaign can create a positive image if those who provide family planning are abusive, condescending, or cavalier to clients or try to pressure them into using a particular method. To succeed, services and products must live up to the positive image created for them.

P.T. Tridaya

US FDA Approves Depo-Provera

The United States Food and Drug Administration (US FDA) approved the injectable contraceptive Depo-Provera on October 29, 1992. The regulatory agency's decision makes the highly effective progestin-only contraceptive available to US women.

Depo-Provera has been widely approved and used around the world for more than two decades (see **Population Reports**, *Hormonal Contraception: New Long-Acting Methods*, K-3, March-April 1987), but it had not been approved in the US. US FDA approval means that the United States Agency for International Development (US AID) will be able to provide Depo-Provera to family planning programs in developing countries. US AID now is making plans to purchase the injectable.

Depo-Provera consists of the progestin depomedroxyprogesterone acetate. The contraceptive dose is 150 mg, administered every three months by injection in the arm. Depo-Provera is as effective as Norplant and the most effective IUD, the TCu-380A.

countries US$23 per set. In addition, medical professionals must be specially trained to insert and remove the implants. As with other new methods, there are also start-up costs for training other personnel and for communication.

Much of the program cost for supplies, training, and service delivery is up-front cost—that is, cost incurred before a woman begins using implants. Voluntary sterilization, too, has high up-front costs. Therefore the cost per couple-year of contraception provided by both methods decreases as length of use increases.

Thus length of use—and client satisfaction, which determines length of use—are crucial to cost-effectiveness. To compare the costs of implants and other methods, planners should average the costs for supplies and services over the years of use. In clinical trials the average length of use for implants was 3.5 years (224), and the implants can be used for as long as five years. In terms of the cost of the commodity alone, Norplant costs somewhat more than a 3.5- to 5-year supply of oral contraceptives, condoms, or injectables and costs far more than an IUD over the period (see Table 1).

A study in the Dominican Republic found that the full service cost per couple-year of protection was greater for Norplant than for the IUD or female sterilization. Researchers at the Asociación Pro-Bienestar de la Familia (PROFAMILIA), the family planning association, considered the costs of personnel and materials for each office visit, the average number of client visits for each method, and the duration of visits. They assumed that Norplant users would continue with the method for an average of 3.5 years, as did IUD users, and that sterilized women receive on average 16 years of contraceptive protection. They calculated that in 1993 the PROFAMILIA clinic would incur costs of US$15 for an IUD, $16 for female sterilization, and $30 for Norplant for each couple-year of protection (12).

Norplant may increase the costs of a family planning organization if women switch from less expensive methods or if they switch from private medical facilities to publicly funded ones in order to obtain Norplant. The study of 550 new Norplant users in 11 Thai hospitals found that 97% of the women would have used another method if implants had not been available. Also, 19% of the women had been buying contraceptives from pharmacies or private clinics but came to a government-funded hospital for Norplant (96). In Thailand the great majority of women who want to control their fertility are using family planning. Where more of the demand for family planning goes unmet, Norplant might attract more new users to family planning and fewer from private sources of contraceptives.

Norplant price. How is the price of Norplant implants determined? The Population Council and Leiras Oy concluded a licensing agreement in 1983. The agreement establishes a formula for setting the price of implants for developing-country nonprofit organizations. Leiras Oy periodically recalculates its price based on its manufacturing and distribution costs, which include labor, materials, factory overhead and depreciation, insurance, and dissemination of information (165). According to the formula, the price for nonprofit organizations cannot be greater than a fixed margin over these costs. This price is available to donor agencies and various organizations in developing countries—governments, government agencies, private nonprofit agencies offering family planning, and other groups offering family planning services at or below cost or without charge. Over the years the price of the implants has risen as Leiras Oy has begun charging purchasers for the full costs of production (118). The price was US$13 in 1986, $18 from 1987 to 1989, and has been $23 since 1990 (243). Prices in the commercial sector in developed and developing countries are not controlled (168). In the US, a set of capsules costs $350.

The current price of US$23 for nonprofit organizations in developing countries covers only the implant set. There are additional costs for shipping, and a trocar that can be resharpened and used for about 50 insertions costs US$6. Including freight and insurance against damage in transit, the International Planned Parenthood Federation (IPPF) charges US$28.58 to its affiliated family planning associations for an implant set not including the trocar (194).

By the end of 1992 Leiras Oy expects to replace the manual process of making implants with a semi-automated process that will increase production. Eventually, increased sales may help to reduce the price, but Leiras Oy first must recover US$23 million spent on developing the manufacturing process and on applications for regulatory approval (168).

Indonesia and China plan to manufacture their own implants in hopes of reducing costs. Indonesia is negotiating with Leiras Oy for a local manufacturing agreement, and China is developing its own implant (75). Local production of other contraceptive supplies has lowered their prices to family planning programs and users (241).

Projecting total commodity cost. Experience is too limited to offer much help in predicting demand for Norplant. In Finland, where a wide variety of methods is available, 3% of contraceptive users have chosen Norplant. Laneta Dorflinger has used this rate to project commodity costs for various countries. She has estimated the number of insertions each year needed to supply 3% of the projected number of users of modern contraceptives in 1995. Her analysis assumes a rate of population growth, number of women of reproductive age, and estimated prevalence of modern contraceptives based on data from the US Bureau of the Census. This analysis also assumes a discontinuation rate of 15% per year for Norplant. In Kenya, for example, there are projected to be 4.3 million women of reproductive age in 1995, with 28% using modern contraceptives. If 3% of these women used implants, 9,935 implants would have to be inserted each year, at a commodity cost of about US$228,500 per year for

the implants only. In Mexico 63,990 annual insertions would be needed to supply implants for 3% of the women who use contraception. The commodity cost would be about US$1.5 million (60). Of course, analysts must adjust such cost projections to local conditions, making their own estimates of the expected level of Norplant use.

Can the Program Provide High-Quality Norplant Services?

Program managers may see Norplant as a new method that will benefit clients, but they also must assess their ability to provide high-quality services (116). Judith Bruce has identified six elements that are fundamental to the quality of all family planning care (35). These six elements apply to Norplant services:

Choice of methods. Clients have different contraceptive preferences and needs. High-quality family planning services offer a choice of contraceptives and provide a reliable supply of all of the methods that they offer. When Norplant is introduced as an additional choice, women should still be told about other methods and encouraged to choose the method that they prefer.

Information given to clients. Providers should give clients accurate information about all available methods and more detailed information about the method that they choose—all in ways that clients understand and find relevant to their needs. When Norplant is introduced, providers should already know and be able to explain how the method works, how it is used, its advantages and disadvantages, the possible side effects, and the insertion and removal procedures (see p. 23). Providers also should be able to help women decide whether Norplant suits their needs and how to take a relevant medical history. Clients must also know where to come for care, the signs that indicate that they should return to the clinic, the schedule of follow-up visits, the date for implant removal, and where to go for removal (see p. 24).

Technical competence. Providers should be competent in performing all necessary medical procedures. Before Norplant is introduced, medical personnel must be trained to insert and remove implants, and support personnel must be trained to maintain aseptic conditions and to handle supplies. Appropriate providers must be prepared to counsel clients about choosing and using Norplant. Sufficient numbers of trained staff must be ready as the program grows and as previously trained staff are reassigned. Systems of supervision and record-keeping should be ready.

Interpersonal relations. Clinic personnel should see their job as helping clients to use family planning. They should have training in understanding the clients' point of view and in communicating with clients in a helpful, friendly manner. If clinic personnel have this attitude and these skills, they can easily offer Norplant in a positive way. Providers should be rewarded for their ability to satisfy clients' needs.

Mechanisms to encourage continuity. Clinics should be prepared to offer clients family planning advice and care over many years. Clients need help with their initial method, and later they may need more information and support if they decide to switch methods. Programs that introduce Norplant need to help women who experience side effects and to conduct routine follow-up visits (see p. 24 and p. 29). Managers must establish an adequate system for implant removal and a strategy for reminding women that implants must be removed after five years (see p. 26 and p. 29). Women who no longer want to use implants need help choosing another method.

Appropriate constellation of services. Clients may prefer that family planning services be offered along with other kinds of services. For example, in some places women may prefer a single service site that offers both family planning and complete maternal and child health services. In other places women may want family planning services offered at job-training sites. Program managers should find out what kinds of services clients would like to receive in combination with family planning and where such services should be offered. In Kenya, for example, Norplant and other family planning methods are offered at clinics set up near marketplaces because that is most convenient for women. Norplant services can be offered wherever technical competence and aseptic conditions can be assured (see p. 28).

With these elements of high-quality care in mind, program managers must assess their program's readiness to add Norplant to the methods already offered. Both the Population Council and WHO provide detailed checklists of the factors that managers should consider when deciding whether to introduce Norplant (164, 258). In making their decision, managers can base their estimates for the cost of training, clinic space, and personnel time on their program's costs for similar expenditures in the past.

Managers must be sure that they can provide their clients with good services before they introduce Norplant. Some family planning programs may decide that they do not have the funds, personnel, or facilities to offer adequate Norplant services now. Others may choose to offer Norplant in only a few locations because of limited resources. Such decisions are consistent with the desire to provide family planning in a manner that serves clients well and uses program resources efficiently. In clinical trials, where high-quality education, counseling, and medical services have prepared women to use Norplant and have given them the best of care, Norplant has been popular. This suggests that Norplant will be popular when the quality of care is good. If clients are satisfied with the care that they receive, they will keep coming back when they need family planning, and they will tell others about their good experiences. Thus managers must be prepared for the costs of offering a popular new method and good services to assure that clients' needs are met, which in turn will attract more users. In contrast, if the quality of care is poor, many people will not use the services, and others will soon discontinue use. If clients are dissatisfied, the money spent on supplies and training will be wasted.

Who Can Help Support Norplant Services?

Donor agencies—particularly the United States Agency for International Development (US AID) and, to a lesser extent, the United Nations Population Fund (UNFPA)—provide most of the contraceptives distributed by family planning programs in developing countries. To date, donor agencies have not supplied Norplant implants in large quantities or funded large training programs because few national family planning programs yet offer Norplant. Most donor support has been for research and introduction activities.

US AID. Since 1981 US AID has helped to support Norplant research and development. This support has primarily been through the activities of the Population Council and also through Family Health International (FHI), the Association for Voluntary Surgical Contraception (AVSC), and other Co-

operating Agencies. US AID is focusing its assistance on 17 large countries, but other countries also may request assistance for Norplant activities, particularly training and technical assistance (37). US AID's Norplant strategy is based on the following principles, set forth in 1990:

- S&T/POP [The US AID Office of Population] will work with designated CAs [Cooperating Agencies] to develop country-specific approaches for Norplant introduction in priority countries.
- To ensure the best use of limited resources, designated CAs will take the lead in training and service delivery, and collaborate with other agencies in conducting related activities.
- Program activities will be those for which A.I.D. has a comparative advantage, such as counseling, training, quality of care, and operations research as they relate to service delivery. The focus of programming will depend in part on the stage of Norplant activity that has already taken place.
- Programs will gradually be phased in with emphasis on providing quality services.
- Widespread promotional activities will not be encouraged since Norplant is a provider- and quality-dependent method and demand for Norplant is expected to exceed AID's ability to supply it.
- [The US AID Office of Population] does not see commodity supply as its primary role and intends to collaborate with other agencies for this purpose. Moderate quantities of Norplant may be procured for assistance to priority programs (244).

Before US FDA approval in December 1990, US AID supported the supply of Norplant only to research programs. US AID did not supply country programs with Norplant until it was approved by the US FDA. In 1992 US AID is filling requests for 29,600 implant sets from 12 countries and has received one request for 3,000 sets in 1993. Plans beyond 1993 will depend on the growth of Norplant use (86).

UNFPA. Since 1986 UNFPA has supported the Population Council's clinical trials and pre-introduction studies in more than 20 countries (89, 242). Also, in Indonesia UNFPA supported a program that provided training and supplies for several methods including Norplant (137). UNFPA provided Indonesia with 164,000 implant sets, the largest number supplied to any country (243). Anticipating future requests to fund Norplant clinical and pre-introduction trials, UNFPA has developed the following guidelines:

- All Norplant trials require national government approval.
- All projects should be developed with an experienced executing agency such as the Population Council, FHI, or WHO.
- The executing agency will supervise all activities and procurements.
- All programs will include wide dissemination of information in the Ministry of Health, other ministries, medical and nursing associations, women's groups, relevant nongovernmental organizations, and other groups.
- All programs should conduct user-attitude surveys (89, 185).

UNFPA supports the Population Council's efforts to introduce Norplant and to develop Norplant II (see p. 7). Activities will include introductory trials, research on client follow-up and cost-effectiveness, and preparation of materials for policy-makers, program managers, and donors (242).

World Bank. The World Bank has made loans to Bangladesh, Indonesia, and Kenya for programs that include Norplant. In Kenya the World Bank is lending funds for a program to provide several family planning methods, and FINNIDA, the Finnish development assistance agency, is funding the portion of the program that provides Norplant training and supplies (85). The 1992–97 World Bank loan to Indonesia for family planning and safe motherhood includes funds for Norplant as part of efforts to widen the variety of family planning methods offered (234). In Bangladesh the World Bank is part of a consortium of donors that will fund family planning and other health services (see p. 22).

IPPF. In 1985 the International Medical Advisory Panel of the International Planned Parenthood Federation (IPPF) approved Norplant and recommended that it be added to the IPPF list of commodities (88). IPPF makes grants to affiliated family planning associations worldwide and subtracts the cost of commodities from the total grant. Between 1985 and 1987 IPPF received requests for Norplant from 35 countries but supplied implants only to 12 countries that met criteria set to ensure quality of care (88). These criteria are:

- At least one doctor trained in insertion and removal procedures, trained counselors, and a system for client follow-up;
- Government registration or else government approval to import implants for clinical trials and training (88).

More recently, the number of sets requested has been small. Requests peaked at over 8,000 sets in 1988 but in 1990 through 1992 averaged about 2,400 annually (88, 133). IPPF officials attribute the decline in requests to increases in the price of the implants and the fact that other family planning commodities are cheaper (88, 194). Some IPPF affiliates receive implants from sources other than IPPF.

Donor coordination. Coordination among donor organizations would improve the continuity of services—a key factor in Norplant programs. For example, when a program plans to introduce implants, one donor might fund training, a second might buy supplies, and a third might provide long-term evaluation. Without assurance that other sources of funding are available to sustain all elements of the program, each donor is reluctant to become involved (99).

In Bangladesh the government has worked with a consortium of donor agencies to develop a coordinated plan for improving health services including family planning (143). Each donor agency identified the most appropriate areas for its participation. For example, US AID has experience in providing resources for training, and the World Bank is able to support the purchase of supplies. In all, 17 donor agencies have agreed to the cooperative program.

In the Bangladesh agreement funds for Norplant are available as part of the amount allocated to clinical trials and the introduction of new technologies. The government of Bangladesh can spend part of these funds on Norplant training and supplies, but the proportion is not fixed. Future demand for each method will determine how much will be spent on each commodity. The original agreement estimated that 20,000 to 30,000 Norplant sets will be needed each year (235).

The concept of a consortium of donors to fund family planning activities, introduced in Bangladesh, is now being applied in Nepal. Within this agreement Norplant would again be offered as part of a much larger program. In 1991 US AID hosted a preliminary meeting of international donors who might be involved in family planning programs in Nepal and elsewhere; more meetings are planned. For organizations such as the World Bank, cooperation is easiest to administer on a country-by-country basis. Other organizations such as US AID may prefer to set global cooperative strategies (131, 132). Similarly, UNFPA has urged a centralized system for procurement and distribution of contraceptive supplies (241).

Keeping the Way Clear for Norplant Users

Where should programs draw the line between tests, procedures, and criteria that are necessary to use a method and those that are unnecessary, arbitrary, and inconvenient barriers that discourage the user? Unnecessary medical barriers—"unnecessary or dysfunctional procedures, practices, policies, and orientations at least partly based on a medical rationale" (199)—diminish the quality of care and limit access to family planning.

There is a pressing need to review guidelines for the provision and use of every contraceptive method and, where necessary, to revise them in light of current scientific knowledge. Introduction of a new method, such as Norplant, offers the valuable opportunity to alert providers so that they can avoid unnecessary barriers from the start and at the same time can assure standards for high-quality care. To date, most programs have not imposed unnecessary restrictions on Norplant use.

Physicians James Shelton, Marcia Angle, and Roy Jacobstein have identified six types of unnecessary medical barriers imposed on various methods (199):

1. Inappropriate eligibility criteria, contraindications, or precautions. Some programs or regulatory agencies may want to apply the same contraindications, warnings, and precautions to Norplant as to the pill. But some warnings about pill use are unnecessary even for the pill, and others may not apply to Norplant. The differences between Norplant and combined estrogen-progestin oral contraceptives—such as Norplant's lack of estrogen and its continuous slow release of very low doses of hormone—may be as important as the similarities. For example, evidence to date does not rule out Norplant for women with thromboembolic disease who cannot use other methods. Eligibility barriers sometimes arise because considerations that providers should weigh along with other factors when advising a woman gradually come to be taken as absolute contraindications.

2. Process hurdles—procedures that clients must undergo that have little or no relevance to use of their method. For example, is an initial pelvic examination really needed for Norplant use? The manufacturer, WHO, US FDA, and some other experts suggest pelvic exams for all women who choose Norplant (94, 174, 258, 259). But a pelvic exam can detect very little relevant to Norplant use except pregnancy, which usually can be determined from menstrual history. Therefore others argue that a required exam will unnecessarily discourage women who, out of modesty, are unwilling to undergo pelvic exams (134). Service sites should offer the best, most thorough care that they can but not force it on clients. Facilities able to conduct pelvic exams *can offer* the exam to a client, explain the exam, its benefits, and its possible help in selecting a family planning method, and let the client choose whether she wants it. She should understand that the pelvic exam is *not required* to obtain Norplant. Service sites that cannot conduct pelvic exams can still offer Norplant.

Similarly, guidelines from a number of organizations assume that service facilities routinely test blood pressure (94, 97, 174, 258, 259). In clinical trials of Norplant, however, blood pressure did not change significantly (see p. 8). Certainly, the test could uncover an important health problem, but should results influence decisions about Norplant use?

Other process barriers include requiring two clinic visits to obtain Norplant or routine follow-up visits every few months, or rigidly insisting on insertion only during menstruation despite other evidence that a woman is not pregnant.

3. Impediments to the eligibility of providers. Studies show that midwives and nurses can insert Norplant as safely as physicians (see p. 28), and they often communicate better with clients. Requiring that only physicians insert and remove Norplant would unnecessarily restrict the method. The quality of care is better enhanced by training providers adequately in the technical skills needed.

4. Provider bias. Because of personal biases, a provider may not describe methods to clients objectively or even may try to override clients' choices. Providers' biases can arise from misinformation or from prejudging clients' preferences. With a new method such as Norplant, providers need to be well-informed from the start so that they do not act on or spread unfounded rumors that discourage clients.

5. Age/parity barriers. No medical reasons prevent a woman from using Norplant because she is young or has no children. In fact, family planning agencies in Baltimore are collaborating to promote and provide Norplant to unmarried, sexually active adolescents who want to avoid pregnancy (264).

6. Regulatory barriers. Some regulatory agencies have been reluctant to approve new contraceptives without local clinical trials (199). Pre-introduction studies are valuable because they develop a core of local expertise often necessary for training and wider use. Repeated effectiveness and safety trials, however, have discovered few if any differences among women and are not likely to yield additional medical information that helps regulatory decision-making.

Avoiding unnecessary barriers enhances the quality of care (199) (see p. 19). First, many of these barriers restrict a client's choice of methods, and convenient access to a choice of methods is a basic element of high-quality care (35). Second, time wasted on unnecessary procedures could be spent instead on important activities such as taking a relevant medical history and thorough counseling.

Family planning programs and facilities vary widely in the services that they can offer. At a minimum, to offer Norplant along with other methods, personnel must be able to take and to interpret a relevant medical history, to counsel potential and current users, to insert the capsules correctly and under aseptic conditions, and to refer users to convenient removal services. Other facilities can offer more, such as removals and pregnancy tests. Both kinds of facilities can offer high-quality care with no need for unnecessary barriers that deny Norplant to women who could use it.

Client Fees

Programs may spread the cost of Norplant by charging users some fee. Volunteer family planning organizations, such as family planning associations, have long charged modest fees for services and supplies (113). The fee must be based on an analysis of what clients are willing and able to pay (125).

Clearly, some women are willing to pay for Norplant. In Thailand some women pay as much as US$8 for their implants, depending on ability to pay (96). In Sri Lanka nearly 85% of the women who were interested in implants were willing to pay US$3 (236). Still, price affects choice of methods. In the Dominican Republic researchers observed that some women who preferred Norplant chose the IUD instead because of its lower price. Because the commodity cost of Norplant accounts for so much of the total price, the Dominican researchers noted that the price of Norplant to users would have to increase greatly if donors stopped supplying the implants (12). In Colombia researchers are studying whether women will pay more for Norplant if prices start low and gradually increase or if they begin at a reasonable but higher level (239).

Planning To Introduce Norplant

Once program managers have decided that their clients will benefit from Norplant and that their program can supply the necessary high-quality services, they must prepare for introduction. For example, managers must consider:

- How big should the initial program be, and how fast should it grow?
- How will people learn about Norplant?
- What does Norplant counseling involve?
- What do insertions involve?
- How should removal services be organized?
- How should Norplant providers be trained and supervised?
- Where should services be offered?
- What record-keeping and follow-up are required?

The Population Council, the Johns Hopkins Program for International Education in Reproductive Health (JHPIEGO), WHO, and other organizations provide detailed information for managers who are planning Norplant introduction (see box, p. 27). Program planners can request these publications for more information on these topics and others.

How Big, How Fast?

Program managers face decisions about how to introduce Norplant services and how quickly to expand them. In the Dominican Republic, for example, the program is small. The family planning association PROFAMILIA carried out clinical trials in Santo Domingo and Santiago. Since pre-introduction trials ended in 1986, PROFAMILIA has continued to offer Norplant. The staff from the pre-introduction trials, now very experienced, continue to provide counseling, insertions, and removals. Although women pay only part of PROFAMILIA's costs, Norplant is still their highest-priced contraceptive option (12, 33). Few women can afford implants, and so the number of insertions remains small. More women might choose Norplant if the price were lower (12). Before Norplant was available in the US, Dominican immigrants requested Norplant at some New York clinics where services are free. These clinics had a waiting list of 500 women by the time Norplant became available (130).

In a larger program in Bangladesh, the Ministry of Health plans to provide implants to 20,000 to 30,000 women each year. Pre-introduction trials started in 1985 under the direction of the Bangladesh Fertility Research Program (BFRP), now the Bangladesh Institute of Research for Promotion of Essential and Reproductive Health and Technologies (BIRPERHT). At first only a few clinics offered Norplant, and BFRP planned gradual growth to 12 and then 30 additional sites. The Ministry of Health, however, now plans a large program to provide long-term methods, including Norplant, nationwide, supported by a consortium of donors (see p. 20).

Program managers need to decide how they can best establish Norplant services that offer both high-quality medical care and thorough counseling, and how quickly they can meet clients' demand for implants. What are the relative advantages of large and small programs and of those that grow quickly or slowly?

In small programs and in those that grow gradually, it is easier to ensure that clients receive high-quality service. Supervisors can monitor newly trained personnel more closely. Training enough providers is easier if the clientele grows gradually. Thorough counseling is easier, too, and women may be able to learn about the method from experienced users. Thus they may make better-informed choices about implants. All of these factors—high-quality medical service, easier management, and thorough counseling—lead to satisfied users.

Large programs and those that grow quickly also have a rationale. Many national programs need to increase contraceptive use in order to lower high birthrates that endanger women's health and impede socio-economic development. In such places policy-makers may want to expand family planning services rapidly, and they may see implants as a valuable part of that effort. Such efforts will be undercut, however, if clients receive poor treatment or are pressured into using a particular method.

Large programs may be necessary to provide removals and offer on-going service to Norplant users, especially if much of the population is mobile. If services are not available nationwide, Norplant users may move where local health care providers cannot serve them. Indeed, in some countries governments are committed to offering the same medical services everywhere. Thus it may be against government policy or politically impractical to offer implants in only a limited number of locations.

The pace at which Norplant services expand must ensure thorough counseling and screening, safe insertions, proper handling of side effects, and adequate access to removal at any time. In most places this will require starting small and growing gradually, learning from experience and adapting the program as it develops. The quality of services depends greatly on how many well-trained providers are available, and training many providers well takes time. Programs that have an existing infrastructure for family planning services with established counseling, conditions for asepsis, follow-up procedures, and communication programs will be able to offer clients this new method more quickly. In any case, a program that chooses to introduce Norplant widely and

quickly must be particularly attentive to maintaining high-quality care.

How Will People Learn About Norplant?

People need to hear about this new method and to learn the facts about it. To help them do so, program managers first need to understand how clients learn about contraceptive methods and then to use this information to communicate with clients. Because women usually first hear about implants and other methods from current users or from medical personnel not involved with implants, these groups need accurate information about the new method.

Women are most influenced in their family planning choices by what they hear outside clinics. Interviewed in Egyptian health centers, 57% of Norplant users listed their relatives, neighbors, and friends as their most important source of information about Norplant (62). In the US as well, women who chose Norplant were more often influenced by friends and family members than by clinic personnel (51).

Thus satisfied users of a particular family planning method often are influential sources of positive information. In Thailand one-third of women who chose implants in clinical trials did so because they had talked with Norplant users (107). Satisfied users also can influence continuation rates. Researchers in the Dominican Republic noted that the earliest users of Norplant were more likely to discontinue because of side effects than women who chose the method several years later. The researchers attributed this change to users' sharing information and supporting each other as well as to counselors' learning more about Norplant and giving clients better information (13). Satisfied users—for example, nurses who use family planning—are particularly credible as providers and counselors.

Conversely, dissatisfied users can discredit a method very quickly. In several countries poor service delivery, especially refusal to remove the implants before five years of use, has caused public opposition to the implant method.

Mass-media television publicity, as well as favorable opinion among users, can attract potential clients, particularly to a new method such as Norplant. In Brazil researchers studied 100 women who chose Norplant and 100 who chose IUDs at the same clinic. They found that 80% of the Norplant users and all of the IUD users had learned about their chosen method before coming to the clinic. Half of the women who chose Norplant—a new method—had heard about it on television. About one-third had heard about the method from friends, relatives, or other women. Of the women who chose the IUD—a well-known method—9% had heard of it on television, and 74% had learned of it from friends, relatives, or other women. Although most women had heard of their method before coming to the clinic, a great majority said that clinic counseling answered questions about the method that they chose (80).

Women also learn about family planning methods from local leaders and community organizations. Government officials, women's health care advocates, religious leaders, and others with a constituency among the public need information about Norplant. Often, they can help design services, too.

Informing other health workers. Health care personnel who are not providing implants themselves nonetheless need to know about Norplant (233). Many women ask questions of family or friends who work in health care. In Brazil, for example, 20% of the women who came for Norplant or IUDs had talked about the method that they wanted with health care personnel outside the clinic (80). Some women ask questions about Norplant when consulting physicians for unrelated reasons. In several cases such physicians misinformed and frightened women because they themselves knew little about the method and were suspicious. In other cases physicians gave women inappropriate care for side effects (262). Health care providers need accurate information about the method including where women should go to obtain implants and to have them removed. Programs can inform health care providers about Norplant by sending them information in special mailings and by including information in journals or newsletters, in in-service education programs, in professional meetings, and in television or other mass media that reach professionals. Conferences and brochures for medical personnel not providing Norplant were part of introduction activities in Egypt and Colombia, for example (111).

What Does Norplant Counseling Involve?

As with all family planning decisions, a woman's choice of Norplant should be an informed choice, freely made. That is, she must know the full range of methods available to her and their characteristics, and she must be allowed to make her own decisions, based on her own needs. The provider must ensure that she has the information and makes her decision without pressure from the provider or from anyone else (42, 172). At the same time, the provider helps the client to recognize her own needs and wants as she makes her decision (see **Population Reports**, *Counseling Guide*, J-36, December 1987).

When counseling accomplishes this, the result is greater initial use of contraception as well as longer continuation of use (see **Population Reports**, *Counseling Makes a Difference*, J-35, November 1987). In the Dominican Republic, as noted, investigators found that, as providers became more confident in counseling, women were less worried about side effects and used Norplant for longer periods (13).

"This woman is interested to see that her friend has just received Norplant." Most women learn about Norplant from other women. Therefore informing the public accurately about Norplant is vital.

Initial counseling can support women's continued use of Norplant in two ways: (1) By informing women beforehand of the method's features and possible side effects, counseling helps to screen out women likely to be dissatisfied with the method and to abandon it early. (2) For those who choose the method, counseling prepares

them for the side effects that they may experience so that they are not frightened if side effects occur.

Telling clients about methods. Clients choosing among family planning methods need to learn the basic features of all available methods. For implants, this includes what they look like and the need for insertion and removal. Women who are seriously considering implants and women who have chosen them need more information, of course. Essential information for both groups is outlined in the "Guide to Norplant Counseling," published with this issue of **Population Reports**. More detailed information can be found in various publications listed in the box on p. 27.

Counseling should emphasize that Norplant is effective for five years and must then be removed, but it can be removed sooner. It should cover the side effects that women might experience. Providers can spend less time on information that women need to hear but not remember, such as how the method works.

Women are asked to understand a great deal of information when they come for counseling. Showing as well as telling can help clients remember. For example, when counseling about menstrual changes with Norplant, some providers in the US show clients calendars marked with possible menstrual patterns, and they point out which patterns are normal for Norplant users as well as which patterns indicate that the Norplant user should return for a check-up (51). Printed material, designed for clients to take home, can be helpful. So can repeating essential information at follow-up visits.

Helping women decide about Norplant. The central step in the counseling process is helping the client choose a family planning method (115). This step has two aspects: (1) helping a woman decide which method fits her needs and (2) assessing whether the method that she wants is medically appropriate for her—that is, medical screening. For both aspects, the provider asks the client questions, and they discusses the answers (see the "Guide to Norplant Counseling").

Questions that help a woman decide if a method suits her needs draw her attention to the features of the method, both positive and negative. For example, a provider might first ask a woman whether and when she wants to have children in the future. If the client wants to delay pregnancy for several years, the provider can suggest Norplant as one of several choices that might be appropriate. The provider should point out that Norplant is effective for up to five years but allows the woman to become pregnant after the capsules are removed. Asking about a woman's experience with contraceptives also can be helpful. For example, if a woman was bothered by irregular bleeding with another hormonal method, Norplant may not be the best choice for her. But for a woman who often forgot pills or does not want to take pills, Norplant might be a good choice.

The risk of sexually transmitted diseases (STDs), including AIDS, is crucial to every choice of contraceptive methods. Providers should always remind clients that Norplant and most other methods do not protect against STDs. Providers should politely ask each woman if she has more than one sexual partner or thinks that her sexual partner has any other sexual partners. If so, she needs encouragement and help to try to persuade him to use condoms at every act of coitus outside marriage. She can use Norplant at the same time for highly effective contraception.

Questions that assess whether a method is medically appropriate ask about symptoms and previous diagnoses. These screening questions should focus on conditions relevant to the contraceptive method and not on general health matters. For Norplant, questions should address whether the client:

- Is pregnant;
- Has active liver disease, as evidenced by jaundice;
- Has cancer of the breast or reproductive organs; or
- Has active cardiovascular disease (see the "Guide to Norplant Counseling").

If questioning reveals that a client has symptoms or a diagnosis of these conditions, or if there is uncertainty, she should be referred to a doctor or nurse for diagnosis and, possibly, treatment before she uses Norplant. The provider conducting the counseling should discuss nonhormonal methods with such a client, should help her choose another method at least for the meantime, and should make sure that she has an ample supply of condoms or spermicide when she leaves.

Prospective Norplant users also should be asked about diabetes, hypertension, migraine headaches, and epilepsy. Clinical studies have not suggested, however, that Norplant use will aggravate diabetes, high blood pressure, or migraine headaches, or will increase the risk of stroke. Still, a number of organizations advise that Norplant users with these conditions may need to be monitored or to monitor themselves (174, 259). They should be referred to a nurse or doctor to decide on this. The recommendation for monitoring is based on findings in some studies that combined estrogen-progestin oral contraceptive altered carbohydrate metabolism or blood pressure or increased the risk of stroke. Also, clinical trials excluded women with diabetes or high blood pressure, and therefore the effects of Norplants on these women have not been studied. As for epilepsy, women who take seizure medication should know that some medications used to treat epilepsy make hormonal contraceptives such as Norplant less effective. They may prefer a nonhormonal method.

Where referrals or monitoring of these conditions is not possible, providers must decide what course of action best protects a client's health, based on the availability of other family planning methods and the client's willingness to use a nonhormonal method such as condoms, spermicides, voluntary sterilization, or an IUD. If she will not use a nonhormonal method, a progestin-only method such as Norplant is preferable to one containing estrogen (94). Leaving a woman without any contraception may be exposing her to pregnancy. Pregnancy, especially frequent pregnancy, can endanger a woman's health. It is particularly dangerous for women with conditions such as cardiovascular disease, diabetes, and cancer. In setting up Norplant services, program managers should take care not to establish strict criteria that arbitrarily exclude certain women. Instead, providers should make balanced recommendations, taking account of an individual woman's situation (see box, p. 21).

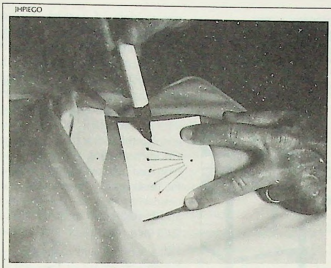
Explaining how to use Norplant. When a woman chooses Norplant, the provider should explain how the capsules are inserted and removed. The provider also should tell the client that she should have the capsules removed after five years but can have them removed at any time sooner. Also, the provider should review common side effects, particularly bleeding changes, so that the client is not alarmed if they occur. Furthermore, the client needs to know the signs of ectopic pregnancy, infection at the insertion site, and cerebrovascular problems that call for her return to a Norplant provider. (See the "Guide to Norplant Counseling.")

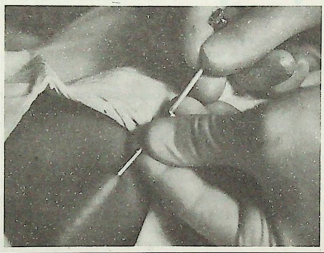
Counseling returning clients about side effects. Providers need to recognize Norplant side effects and know how to

manage them. When a woman reports a problem, the provider should determine, if possible, whether it is due to Norplant or to some other cause, and what course of action to follow. Both JHPIEGO and the Program for International Training in Health (INTRAH) provide check lists for diagnosing the causes of common conditions experienced by Norplant users (94, 97) (see box, p. 27).

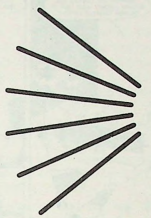
The most common Norplant side effects are menstrual changes—spotting, amenorrhea, or frequent, prolonged, or heavy bleeding (see p. 5). For the great majority of clients whose bleeding changes pose no health risk, counseling may be what is needed. Some women simply want an explanation. Others fear for their health. In these cases, the provider can assure the client that these changes are common and pose no health risk. If the woman is not reassured, she may want to choose another method. Some women find that the bleeding interferes with their religious obligations or their sexual relations with their husbands. When women have doubts about continuing Norplant use, the provider should help them weigh the advantages and disadvantages of switching to another method.

JHPIEGO





Courtesy of Wyeth-Ayerst



The template above can help providers position Norplant capsules correctly. The provider places the template against a woman's arm and marks the ends of the six slots on her skin with a ball-point pen or similar marker (see upper photo). When inserting the capsules using the trocar, the provider lines up each capsule with one of the marks (see lower photo). Capsules should be inserted just under the skin.

Who can counsel? Various program staff may be responsible for counseling. In most places nurses counsel women in groups at the clinic and then counsel them individually. In Indonesia the family planning field worker does much of the preliminary counseling about the range of methods (253). Physicians in private practice may counsel clients themselves. Whoever has the chief responsibility for counseling, almost all health care providers counsel clients, informally or formally, at some time, and therefore they need training in counseling skills and talking sympathetically with clients (97).

What Do Insertions Involve?

To set up services, managers must understand what Norplant insertion requires. In brief, to insert an implant, the provider anesthetizes an area of the skin on the inside of the woman's upper arm. The provider then makes a 2 mm incision, either with a special trocar, if it is sharp (49, 53), or with a scalpel, and uses the trocar to insert the capsules just under the skin. The trocar is marked to indicate how far it should be placed under the skin to insert each capsule. The provider places the capsules in a fan shape, radiating out from the incision. Using a paper or plastic template to mark the pattern of the implants on the woman's skin helps to insure correct placement of the anesthetic and the implants (82) (see photos above). Placing the capsules just under the skin, not deeply, helps to assure that they can be removed easily later (233). When all six capsules are in place, the provider closes the incision with an adhesive bandage—no stitches are needed—and places compresses and gauze over the entire area. Insertion usually takes 8 to 10 minutes (6). The Population Council, JHPIEGO, INTRAH, and WHO have published complete instructions for insertion and removal (94, 97, 149, 258).

Insertion and removal of implants are minor surgical procedures. The Population Council and Leiras Oy developed the techniques for insertion and removal (149). As experience with Norplant grows, practitioners are suggesting modifications of these techniques (49, 51, 97). Most of the equipment for insertion and removal is commonly used in health centers. Leiras Oy provides the specially marked trocar. Norplant insertion and removal kits supplied by US AID contain all the necessary equipment (37).

Avoiding infection. Providers should wash their hands and use gloves that have been soaked in a 0.5% chlorine solution for 10 minutes or boiled in water for 20 minutes. Equipment should be sterilized. Where sterilization is not possible, high-level disinfection can be done by boiling instruments for 20 minutes or by soaking them in chemical disinfectants (97, 149, 258). If the health care provider wears gloves and avoids cuts with instruments that have blood on them, he or she should be safe from any infection borne in clients' blood, such as AIDS or hepatitis B.

A pamphlet from the Philippines illustrates two choices for Norplant users: At left, after five years using Norplant, a woman receives another set of implants to continue contraception. At right, another woman has the capsules removed to become pregnant.

Timing of insertion. To ensure that clients are not pregnant, their implants should be inserted during or within a few days after a menstrual period, or after abortion, unless other information indicates that they are not pregnant. Norplant is effective within 24 hours. Women who are breastfeeding are advised to use a barrier method of contraception (97, 150). Still, women can safely use Norplant after the first six weeks of breastfeeding, and research may establish that even earlier use is possible (2, 55, 56, 147, 188, 189, 196, 256).

How Should Removal Services Be Organized?

Program managers must understand the procedure involved in removing implants. To remove the capsules, the provider finds them by feeling them, injects local anesthetic under the capsules, and makes one 4 mm incision near where the insertion incision was made. With fingers, the provider pushes against the skin, moving one capsule at a time toward the incision and then, with mosquito forceps, pulls out the capsule. Any fibrous tissue around the capsule must be scraped away with gauze or a scalpel as the capsule is removed. After all of the capsules are removed, the provider places an adhesive bandage and compresses over the incision site (97, 149).

Removals take longer than insertions, and they are more likely to be difficult. They should be done in a clinic setting. In an Indonesian study of removals, the mean time required was about 22 minutes (6). Occasionally, removals can take an hour or even longer (83, 107). Rarely, the provider may need to ask the client to return for a second visit if removal is so difficult that her arm becomes swollen (166). Removals are more likely to be difficult if the provider is not skillful, the implants are deep in the arm, or fibrous encapsulation is extensive. The woman's arm may be painful and bruised after removal (111).

When to remove the implants. The capsules should be removed after five years of use or whenever a woman wants them removed for whatever reason. In addition, providers may recommend removal for such medical reasons as pregnancy; signs of possible cardiovascular disease; possible anemia related to heavy bleeding; implant expulsion, which will require replacement with sterile capsules; severe infection or abscess at the insertion site; and cancer of the breast or reproductive organs. In clinical trials some Norplant users asked providers to remove their implants for conditions, such as irregular bleeding or mild weight gain, that did not impair their health. Initial counseling should try to screen out women who think that they could not tolerate such side effects. Good counseling also may help a woman who has chosen Norplant but now wants it removed. In some cases it may be the husband who needs reassurance, and he should join the counseling session. The provider can listen to the woman and her husband, provide reassuring information, and discuss their options, of which removal of the implants is one.

Other women will request removal because they want to become pregnant or they are moving to an area without Norplant services. Again, initial counseling and screening can minimize the number of such women who choose Norplant. People's circumstances change unpredictably, however, and women cannot be denied removal just because they change their minds or their situations change.

Access to removal. After counseling, some women still will want Norplant removed, and they should be accommodated. In focus-group discussions, however, some users report difficulty persuading health care providers to remove implants (262). Health care providers have given various reasons for refusing or delaying removals. Removals require time and aseptic conditions, and clinic staff may not be able to perform them whenever a woman comes in (233). In other cases providers may not feel confident of their ability to perform removals (262). In still other cases providers have disagreed with women who complained that their side effects were so severe as to require removal. Clinic personnel also have refused removal because implants are expensive, and they thought that women had had sufficient warning about side effects before they chose implants.

Access to removal is a necessary part of high-quality service, however. Women should not be forced to continue using implants if they no longer want them. Such a policy is intrinsically unethical, and word of such a policy will discourage women from trying the method.

As Norplant becomes available, managers must plan for removals by ensuring that facilities and trained personnel are ready when needed. Program managers also must ensure the following six conditions:

- During initial counseling providers must tell women: (1) where to go for removal; (2) that removal is necessary after five years of use but can be done sooner at their request; and (3) that they must return to the clinic if they are moving from the area. Staff should remove the implants if the woman is moving to an area without implant services.
- Clinics designated as removal facilities must allocate time, space, equipment, and personnel to removals.
- Staff must know either how to remove implants or where to refer women.
- Staff must agree that women can have their implants removed on request.
- Staff trained in implant insertion, removal, and counseling should not be transferred elsewhere until other trained staff are available.
- Clinics should have established back-up procedures for difficult removals.

Resources for Program Managers

Supplies

International Planned Parenthood Federation
Regent's College, Inner Circle, Regent's Park, London NW1 4NS, UK
IPPF provides supplies to its affiliates only, at a cost of US $23.12 per implant set, including one trocar per 50 implant sets.

US AID
Office of Population, Washington, D.C. 20523, USA
US AID provides supplies only for projects supported by a US AID mission or conducted with a Cooperating Agency.

UNFPA
220 East 42nd Street, New York, New York 10017, USA
UNFPA provides Norplant supplies only in the context of official projects negotiated with national government health authorities.

The manufacturer also provides implants.

Leiras Oy Pharmaceuticals
P. O. Box 325, SF - 00101
Helsinki, Finland

Publications listed below are available free of charge unless otherwise noted.

General Information

Norplant: A Summary of Scientific Data. The Population Council, 1990. 39 pp.

Norplant Worldwide (Newsletter). The Population Council, Two 4-page issues per year.

"Norplant at a Glance" (Information sheet). Population Information Program, 1992. 1 p. (See copy mailed with this issue of **Population Reports**.)

Program Operation Guides

Norplant Contraceptive Subdermal Implants: Managerial and Technical Guidelines. World Health Organization, 1990. 134 pp. Cost: US$12.50.

Norplant Guidelines for Family Planning Service Programs. The Johns Hopkins Program for International Education in Reproductive Health (JHPIEGO), 1992. Available in English, French, and Spanish. 150 pp. Cost: one copy free to US AID-funded projects; write for cost of additional copies.

Training Materials

Norplant Contraceptive Subdermal Implants: Guide to Effective Counseling About Norplant. The Population Council, 1989. 38 pp. Available in English, French, and Spanish.

Norplant Prototype Training Curriculum. The Population Council, Program for Appropriate Technology in Health (PATH), Family Health International, and Association for Voluntary Surgical Contraception (AVSC), 1990, revised 1992. Available in English and French from the Population Council.

Norplant Brochure for Physicians. PATH. Available in English and Spanish.

Norplant Implants: Manual for Clinicians. The Population Council, 1990. 40 pp. Available in English, French, and Spanish. Cost: US$3.50 plus postage.

Norplant Training Course Outline: Standard 3-Day Course. JHPIEGO, 1992. Available in French and English. 40 pp.

Norplant Course Handbook: Guide for Participants and Trainers. JHPIEGO, 1992.

Guide to Norplant Counseling. Population Information Program, 1992. (Mailed with this issue of **Population Reports**.)

Prototype Client Record Form for Norplant. AVSC, 1992. 3 p.

Norplant Slide Set. Insertions and removals. JHPIEGO, 1992. 100 slides cover basics of Norplant counseling, insertion and removal techniques, and troubleshooting for insertion and removal problems. Available in English, French, and Spanish. Cost: one set free to US AID-funded projects; write for cost of additional copies.

Norplant Training Video. Insertions and removals. JHPIEGO. Available in late 1992.

Norplant Insertion and Removal Practice Training Arm. PATH. Cost: $13-$16 each, depending on quantity.

Norplant Prototype User Brochures. PATH. Available in English, Indonesian, Sinhalese, Spanish, Swahili, and Tagalog.

Norplant Training Videotapes. Leiras Oy Pharmaceuticals. Available in English. **Slide sets** available in English.

Addresses

Association for Voluntary Surgical Contraception (AVSC)
79 Madison Avenue, New York, New York 10016, USA

The Johns Hopkins Program for International Education in Reproductive Health (JHPIEGO)
Brown's Wharf, 1615 Thames Street, Suite 200, Baltimore, Maryland 21231, USA

Leiras Oy Pharmaceuticals
P. O. Box 325, SF - 00101 Helsinki, Finland

The Population Council
One Dag Hammarskjold Plaza, New York, New York 10017, USA

Population Information Program
The Johns Hopkins Center for Communication Programs, 527 St. Paul Place, Baltimore, Maryland 21202, USA

Program for Appropriate Technology in Health (PATH)
4 Nickerson Street, Seattle, Washington 98109, USA

World Health Organization
1211 Geneva 27, Switzerland

Organizing removal services. Removal services can be organized in several ways. All clients requesting removal might be referred to a central facility; a team of trained providers could travel to service sites on specified days; or many providers could be trained to remove implants at many sites. In deciding how to organize removal services, managers must consider the convenience of clients and how best to train providers and to maintain good medical services. A new program will generate few requests for removal and thus will offer few chances for providers to perform or observe the procedure. A centralized facility for removals or a traveling team with a specific schedule would be suitable for a new program. These skilled providers could schedule removals so that trainees would be able to observe the procedure and perform removals under supervision. Centralized facilities should be conveniently located, however, within easy reach of most clients.

As the number of Norplant users increases, demand for removal services will grow. At that point, most providers could be trained in the removal procedure. Removal services should not be spread so thinly, however, that providers do not perform enough procedures to maintain their skills.

How Should Norplant Providers Be Trained and Supervised?

Health care personnel need different kinds of information about Norplant. Those who are not involved in implant services need a general introduction to the method so that they can answer questions and refer clients (see p. 23). If

implants are to be widely available, information about Norplant should be part of all preservice family planning education. In Thailand and Indonesia all physicians, nurses, and midwives receive a general introduction to Norplant and other family planning methods while they are in school (75).

Personnel directly involved in implant procedures and counseling need special training and practice to develop skills. In-service training is necessary to supply trained personnel to an expanding program. In clinical trials the personnel who inserted implants were trained at Population Council centers in Indonesia, Egypt, and the Dominican Republic (25). These providers, primarily physicians, in turn trained people in their own countries. Other countries planning to introduce Norplant need a similar core group of trained and experienced providers. The group can continue to train other providers as the program expands (9). Some can receive further instruction and become trainers, perhaps using their clinics as training sites. A high-quality program depends on well-trained providers, and managers should encourage good training by recognizing and rewarding good trainers (134).

Formal training must continue as programs grow. As implants become more widely available, more clinic staff will learn both medical procedures and counseling informally, by watching experienced personnel work. This informal training-by-observation is not reliable and must be supplemented with formal training (9).

Training for removals presents special problems because, when implants are first offered, few women request removal (233). A trainer may demonstrate a removal, but trainees may have no opportunity to perform one until months or even years later. Strategies to help ensure high-quality removals include referring all women to a central facility for removals, providing trained practitioners with a videotape of the procedure, having a trainer go out to clinics on request, encouraging practice on model training arms or animal tissue such as chicken breasts, and retraining clinic personnel later as the need for removals grows (134, 233, 252).

Después de 5 años, la protección del NORPLANT termina. Ud. debe visitar de nuevo al médico en _____ (mes/año) para que él le saque el NORPLANT, le inserte uno nuevo si Ud. quiere o bien, le ayude a cambiar de método.

Adapted from PATH in collaboration with the Population Council

A page in a Latin American pamphlet explains to the Norplant user when to have the implants removed. The provider writes the month and year on the blank line provided.

In Indonesia, Thailand, and elsewhere, nurses and midwives, as well as physicians, have performed Norplant insertions and removals. Two Indonesian studies compared insertions and and removals performed by physicians with those performed by nurses and midwives (6, 212). They found no significant differences between the two groups in the length of these procedures or in insertion-site infection rates. In the US, physicians, nurse practitioners, and nurse-midwives are being trained (252). When nurses and midwives offer Norplant, more women can receive implants, and the cost may be lower. In many countries Norplant will be widely available only if nurses and midwives provide the method.

Supervision. Good initial training is necessary but not sufficient to ensure continued high-quality service. In addition, managers must continually supervise staff. Supervision should cover clinic services, clinic management, and interaction between client and provider (98). Different personnel may have responsibility for supervising each of these areas. Initially, trainers might supervise services, especially clinical care. Program managers must develop service standards (100). Manuals prepared by JHPIEGO and WHO suggest standards for evaluating services (97, 258) (see box, p. 27).

Supervision of Norplant services will be most effective as part of a good overall supervisory system. When a good supervision process is in place, Norplant services can be reviewed as all other services are reviewed (98). Separate supervision of Norplant services may be necessary if there is no general system or as the new method is introduced.

Regular supervision helps maintain high-quality service. Researchers in Ecuador concluded that insertions seemed deceptively easy to some clinic staff. Eventually, overconfidence led to carelessness and cases of infection at the insertion site. With periodic supervision, the situation was corrected (126).

Where Should Services Be Offered?

In general, any facility that can offer voluntary sterilization or IUDs also can offer implant insertions and removals (36). The room must be clean and equipped with sterile or high-level disinfected supplies (7, 97). In addition, a service site should have the personnel and the space to counsel clients, including a place for client and provider to talk privately. Service points also need adequate record-keeping capabilities.

More service sites will make Norplant more available, but quality of care must be maintained as services expand. In Kenya 83% of women live in rural areas (103). To serve them, clinics offering vaccinations, child health services, and several contraceptive methods have been set up in rural marketplaces (66). Although these clinics lack on-site facilities for sterilizing equipment, a physician has devised a way to offer Norplant insertions there without sacrificing the quality of care (153). Every Monday several presterilized packets, each containing the equipment and supplies for one insertion, are delivered to each clinic where there is a trained provider. On the following Monday the packets of instruments that have been used and any that remain unused are taken back to Nairobi for autoclaving. New packets are left. There were no cases of infection at the insertion site in a study of the first 300 insertions performed at these marketplace clinics (153). In Indonesia thousands of women received implants and IUDs in temporary outreach facilities set up in urban and rural markets, neighborhoods, or fairgrounds. These programs reached many women who were not using modern birth control methods (181). In 1990 more than half of the women who received Norplant were served in such clinics (92). Temporary clinics can present special problems, however. BKKBN and the Ministry of Health have recently discontinued Norplant insertions in temporary clinics because of concern about the ability to maintain asepsis, to screen clients adequately, and to keep records (92, 253).

What Record-Keeping and Follow-Up?

What records must be kept about Norplant users? Initially, clinic staff need to record the name of each implant recipient and when her implants need to be removed after five years of use. At any follow-up visits, any complications or side effects should be noted. When her implants are removed, that, too, should be recorded.

In addition to helping serve individual clients, record-keeping helps program managers evaluate the use of implants. Records on infections at the insertion site and removals for pre-existing conditions such as pregnancy help managers to assess the quality of medical procedures and screening. Also, managers need continuation rates to determine the cost of the program per couple-year of protection from pregnancy.

Organizations involved in Norplant introduction suggest follow-up visits about one month after insertion and once a year thereafter (94, 97, 176, 198, 258). At the first visit the provider should make sure that there is no infection around the area of the implants, answer the client's questions, and again discuss possible side effects, the need for removal after five years, and the availability of removal whenever the user wishes. At the client's annual visits, the provider should answer the client's questions and screen the client for conditions that might require removal of implants or monitoring of the client (94, 97). Women with diabetes or high blood pressure may require more frequent follow-up visits to monitor their condition (see p. 24). AVSC has developed a prototype client record form for keeping track of the client's health for the full five years of implant use. The form is a record of the client's name and address, medical history, and physical condition. It can be updated on each follow-up visit (17).

How will Norplant users recall when to have their implants removed? If women come in for a yearly check-up, both they and the program are more likely to remember removal after five years. Most programs also give women some written statement of the date for removing implants. In Indonesia and Nepal, for example, program clients have family planning cards, and Norplant users' cards show the removal date (28, 66). In Finland and elsewhere the provider attaches a reminder card to the woman's file and gives her one to keep. In other programs the provider writes the removal date on the information booklet that the woman receives (151).

Keeping track of women who have received implants has been difficult (7, 24, 122, 187, 262). Programs may choose to emphasize the client's responsibility to return for implant removal. To assist her memory, she could be given a colored card that states the date to return. Each year's card would be a different color. Radio announcements, clinic posters, or other means would tell women that this is the year for women with a particular colored card to have their implants removed (20, 37). In some countries, particularly if the population is mobile, broadcast announcements can remind women to have their implants removed.

New Method, New Opportunity

Introducing a new family planning method such as Norplant is an opportunity for program managers to improve clients' satisfaction and thus program performance. Pre-introduction trials have shown that women like the method if it is offered with good medical care and counseling and if they can have the implants removed when they choose. If a program provides high-quality services and publicity that positions the method to meet clients' needs, Norplant may become a popular new family planning method.

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2. Purpose: _____

Development of a Contraceptive vaccine for use by the Human male - Results of a feasibility study carried out in Adult Male Bonnet Monkeys - N R Moudgal, G S Murthy, N Ravindranath, A J Rao & M R N Prasad.

MALE CONTRACEPTION

In the case of the male, as yet no method has been found that is fully effective, safe, reversible and acceptable. Several factors are responsible for this constraint. Foremost among there is the incomplete understanding of the physiology of the male reproductive system and the relative lack of suitable targets for fertility interference in the male as opposed to the female. Another factor is the debatable issue of the requirement of drug induced azoospermia as a prerequisite for a male contraceptive. On the question of safety the risk versus benefit considerations of a male contraceptive require greater safety standards than those accepted for therapy of other clinical disorders. That may indirectly apply to women) out there is reason to believe that future research will lead to a better understanding of male reproductive physiology and to the discovery of safe, reversible and easily acceptable male anti fertility agents.

It is anticipated that with the advancement in the field of ~~xxxxxx~~ molecular and cellular biology and genetics, a fuller knowledge of the male reproductive system will create opportunities for more rapid development of better methods of male contraception.

The earliest report of attempts at chemical control of male fertility was concerned with the use of the male hormone itself. (Testosterone - years studied - 1949-52) This study was succeeded by investigations

of a variety of non hormonial agents with testicular action some of which reached clinical testing before being abandoned. With the advent of oral contraceptives for women, the effect of new progestogens was assessed in man. A non steroidal inhibitor of pituitary function methallibure also reached clinical trial. More recently androgenic steroids such as danazol or progestational steroids and testosterone either alone, or in various combination have been studied.

Steroidal Contraceptives:

DMPA injections in doses of 1000 mg per one or two weeks to human males induced azoospermia by 70 days which lasted for several months. The effects were reversible by six to eight months following withdrawal of treatment. However libido and sexual potency was affected.

Medioxy Progesterone Acetate in combinations with andrógen were conducted at several centres supported by WHO, Population Council and Ford Foundation. Testosterone was added to ensure libido and sexual potency. Some centres evaluated the effect of DMPA plus testosterone enanthate (TE) or cypionate (TC) both injected once monthly with DMPA in monthly doses of 150 mg or higher plus TE of 250 mg or 400 mg. This induced oligospermia or azoospermia in majority of volunteers. In another study a combination of 200 mg DMPA plus 250 mg TC once monthly produced azoospermia in 56% of men within 6 to 15 weeks the remaining men achieved oligospermia within 20 weeks. Cyproterone Acetate also induced severe oligospermia or azoospermia but affected libido in at least a few of the volunteers.

The NIHFW also administered Cyproterone Acetate orally at a dose of 20 mg daily and testosterone enanthate at a dose of 250 mg every fortnight to five volunteers. The test were successful but the efficacy of the pills cannot be proved unless multi-centre trials are initiated and conducted.

Microsdose Intravaginal Levonorgestrel Contraception:-

A multicentric clinical trials - Contraceptive Efficacy and side effects - W H O - Task Force on long Acting systems Agents for Fertility Regulation.

Participants - Thailand, People's Republic of China, India, Columbia, Switzerland, Cuba, Brazil, Pakistan, USSR, U K, Zambia, Sweden, Tunisia.

A multicentric clinical Trial - 19 centres - (Largest participation China, follwed by India and Brazil) in 13 countries - to assess the contraceptive efficacy and clinical acceptability of silastic 382 vaginal ring releasing 20 mg of levonorgestrel for at least 90 days.

1005 women, 8176- 74 women months.

Since 1918 vagina recognised as a suitable site for administration of drugs that will reach the systemic circulation. In a patent issued to Dr. Gordon Duncan of Upjohn Ltd in 1968 it described a vaginal ring composed of silicone polymer which could release a number of progestational steroids for contraceptive purposes.

In the first study (1970) three women had a vaginal ring releasing medroxy progesteron acetate placed in the vagina for 28 days. Although ovulation was suppressed the ring design was such that the drug was homogeneously mixed with the polymer which resulted in a pronounced initial release of the drug.

Research undertaken by the W H O special programme of R+D &

Research Training in Human Reproduction has aimed at the development of the low dose progestogen only approach with a minimum of ovulation inhibition but relying upon local pharmacological effects on the ~~cervical~~ Cervical mucus and endometrium. Initially the W H O research concentrated upon progesterone itself, norethisterone and levonorgestrel. However as a result of excessive menstrual disturbances and too many involuntary pregnancies, progesterone and norethisterone rings were abandoned. These results led to the selection of a vaginal ring which released 20 mg/day of levonorgestrel.

This multicentre study was undertaken between 1980-86 in 19 centres in 13 countries. The trial was approved in all centres by the local institutes ~~either~~ ethics Committee and by the national drug regulatory authority. Women attending the institutes family planning services were invited to participate in the study and were fully informed as to the nature of the trial, its potential risks and benefits.

Each ring weighed approximately 11 g. Manufactured from silastic medical grade 382[R] polysiloxane elastomen supplied by Dow Corning, Midland, Michigan, USA. The levonorgestrel was supplied Schering AG, Berlin (West). Rings were manufactured by Lemery S.A. Mexico city.

A total of 1005 women were admitted only 2 and 4 subjects were recruited in Bangkok and Karachi. In these centres the vaginal ring was perceived by the subjects as unaceptable prior to admission to the study as its insertion required genital manipulation.

Reasons - for discontinuation - The 12 month discontinuation rate for all reasons is 50.3%. Africa - 68.1%, Asia - 59.9%, China - 31.7%, Europe - 45.8%, Latin America - 57.1%.

Contraceptive Efficacy -

A total or 26 pregnancies with the ring in place and one of these was ectopic. Six resulted from unprotected intercourse, five cases the ring had been removed by the subject and in one case the pregnancy was associated with unnoticed expulsion. So the combined total pregnancy rate at one year is 4.5%. The "protected" pregnancy rate of 3.7 is higher than that reported for the Population Council's combined levonorgestrel estradiol releasing ring. But this levonorgestrel only ring in this study was designed so as to avoid the concomitant administration of estrogen to the ~~provial~~ Cervical and vaginal ~~mucosae~~ Mucosae. This ring has a pregnancy rate which is comparable with the low dose combination pill and much lower than that found with the levonorgestrel mini pill in previously published W H O randomized multicentre studies.

Outcome of pregnancies - Of the 26 pregnancies that occurred with the ring in place, 19 were terminated by induced abortion, one ended in spontaneous abortion, one was an ectopic pregnancy and one patient was lost to follow up.

Reasons for discontinuation - Table III cumulative discontinuation rates at one year.

Reasons for discontinuation	Number of events	Rate at one year per 100 women
Pregnancy	32	4.5
Menstrual problems	138	17.2
~~Problems~~	~~109~~	~~14.0~~
Other medical reasons	109	14.0
Non medical reasons	77	10.8
Expulsion	57	7.1
Loss to follow-up	99	12.7

The principal reason for discontinuation was "menstrual problems" and with this group, intermenstrual bleeding (6.2%) xax and prolonged xexsxn menses (4.6%) were the commonest. In comparison the gross rates quoted for the Population Council ring were 11.5% and 8.9% which are lower than the rate in the W H O trial. This was to be expected as combination oral contraceptive rates have much lower discontinuation rates for menstrual irregularities than progestogen only oral contraceptives. It is also reasonable to expect that a vaginal method of contraception will have higher subjective complaint rates as has been shown in the randomized comparative study of the population Council vaginal ring and the oral contraception in which the women using the ring had complaint rates of 34.1% and 37.8% compared to 9.8% in the O C users.

Microdose Intravaginal Levonorgestral Contraception - A Multicentre clinical Trial - Expulsion and Removals - W H O .

Expulsions - leading to discontinuation

57 discontinuations of method due to expulsion giving a one year discontinuation rate of 7.1%. Majority of discontinuation for expulsion occurred within the first 3 months of ring use. There is considerable heterogenity with a rate of 1.7% for Europe and 22.9% in Asian women.

Number of Expulsions -

In total 771 women did not expel their rings for a total study time of 558 years.

The other 278 expelled the ring at least one although details are not available for 44 women. Thus 234 women (24.2%) experienced a total of 504 expulsions of the vaginal ring.

Distribution of the number of expulsions of the vaginal ring.

No. of expulsions	No. of women (%)	women months of use
0	771 (76.7)	6186
1	150 (14.9)	1259
2	40 (4.0)	361
3	24 (2.4)	178
4	6 (0.6)	57
5	5 (0.5)	53
6	4 (0.4)	38
7	4 (0.4)	33
10	1 (0.1)	12
Total	1005	8177

In 417 (83%) expulsion the circumstances of the event were noted. The majority of the expulsions coincided with defecation (57.3%) with for fewer at urination (11.5%) at menstruation (16.8) during strenuous activity (5.3) and intercourse (1.9). It can be seen that there are large regional, differences, women in Asia and China have almost twice the first expulsion rates of the other regions. Therefore the particular reason for first expulsion varies from region to region.

Removal of the ring by the women herself was reported by 121 women on a total of 201 occasions of which 190 had clinical details

provided. The removals took place in 12 centres (there were non in 7 centres) and 4 centres contributed 100 of the subjects reporting one or more removals and 83% of the episodes of removal.

The commonest "medical" reasons given for removal were pain or bleeding (2o subjects) or vaginal discharge or ~~irritation~~ irritation (26 subjects) less than 1% of the subjects removed the ring because of coital discomfort (dyspareunia). The vast majority (68/69) of the removal took place for unrelated reasons occurred in subjects in 4 centres. There were no removals by the Asian women low rates in Africa and China and high in Europe. In Latin America there appeared to be a large variation from centre to centre.

It should be noted that the four centres in China, two of the three centres in India (Chandigarh/New Delhi) and the Brazilian centre contributed 52.2% of the subjects recruited and 55.1% of the women months experience with the device but 71.5% of the women who had an expulsion for which details are available.

WH 3.33

-Microdose Intravaginal Levonorgestral Contraception:-

A Multi Centre clinical trial - Bleeding patterns - comparison with other reasons for discontinuation.

Cumulative discontinuation rates & one year ~~reasons for~~ duxon discontinuation

REASONS FOR DISCONTINUATION

	No of events	Rate at one year per 100 women
Pregnancy	32	4.5
Menstrual problems	138	17.2
Other medical reasons	109	14.0
Non Medical Reasons	77	10.8
Expulsion	57	7.1
Loss to follow up	99	12.7
Total	512	50.3

Study on Bleeding Patterns:-

Out of the total of 1005 women who entered the study from 19 centres 702 were provided with a menstrual diary with a daily record of the occurance of bleeding/spotting or neither. The clinically unacceptable patterns are -

no bleeding throughout the reference period prolonged bleeding;
at least one bleeding/spolting episode lasting more than 14 days;

frequent bleeding; more than 5 bleeding/spotting episodes;

infrequent bleeding; 1 or 2 bleeding/spotting episodes;

irregular bleeding; 3 to 5 bleeding/spotting episodes and less than 3 bleeding/spotting free intervals of 14 days or more;

combination of the above categories

Clinically acceptable pattern.

None of the above, that is a pattern with 3 to 5 bleeding/spotting episodes none longer than 14 days and at least 3 bleeding/spotting free intervals of 14 days or more.

No. of Diaries	Reference	Period	
I	II	III	IV
days 1-90	days 91-180	181 - 270	271 - 360
702	586	510	449

Number of women (percentage) experiencing different types of bleeding patterns in each reference period.

	Reference Period			
	I	II	III	IV
Bleeding patterns	days1-90	days90-180	days 181-270	days271-360
Irregular	157 (22.4)	164 (28.0)	145 (28.4)	116 (25.8)
Infrequent	54 (7.7)	52 (8.9)	52 (10.2)	33 (7.3)
Frequent	80 (11.4)	~~353~~ 53 (9.0)	28 28 (5.5)	35 (7.8)
Prolonged	5 (0.7)	1 (0.2)	3 (0.6)	4 (0.9)
Prolonged & irregular	35 (5.0)	21 (3.6)	11 (2.2)	9 (2.0)
Prolonged & infrequent	5 (0.7)	4 (0.7)	0 (0.0)	4 (0.9)
Prolonged & frequent	5 (0.7)	1 (0.2)	2 (0.4)	2 (0.4)
No bleeding	6 (0.9)	7 (1.2)	4 (0.8)	7 (1.6)
Unacceptable patterns	347 (49.4)	303 (51.7)	245 (48.0)	210 (46.8)
Acceptable patterns	355 (50.6)	283 (48.3)	265 (52.0)	239 (53.2)

This table shows the percentage experiencing clinically important bleeding pattern irregularities as reflected by their menstrual diaries in each successive reference period. Approximately half the women experience "unacceptable" patterns in each reference period, the commonest problem being "irregular bleeding in one quarter of all women. It should also be remembered that women with more disruptive patterns discontinue use early and are therefore under represented in the later reference periods.

The following table shows the No. of women experiencing clinically important bleeding patterns in their discontinuation reference period by reason for discontinuation. It is clear that even among the 443 women who completed the study 230 (51.9%) of these experienced "unacceptable" patterns, half of these being irregular bleeding. The table also shows that of the 9 women who became pregnant, 5 experienced an irregular bleeding pattern during the time preceding conception. Of the 72 women discontinuing method use for "desires pregnancy" all but four have "unacceptable" patterns but in the case of 75 who had v vaginal problems, 41 were in the "acceptable" pattern.

Number of women experiencing different types of bleeding patterns in the discontinuation (1st) reference period.

Discontinuation reasons	1 No bleeding	2 Prolonged bleeding	3 Frequent bleeding	4 Infrequent bleeding	5 Irregular bleeding	6 Prolonged & infrequ-ent blee-ding	7 Prolonged &irregu-lar bleed-ing	8 prolonged & frequ-ent bleeding	9 Acce-ptab-le patt-ern	10 Total
End of study	6	3	57	32	117	4	10	1	213	443
Pregnancy	-	-	-	-	5	-	-	-	4	9
Bleeding problems	1	-	2	1	8	-	-	-	6	18
Amenorrhhea	-	-	4	1	2	1	-	-	7	15
Pain	1	-	4	1	5	-	1	-	9	21
Vaginal problem	-	-	11	6	17	-	-	-	41	75
Other medical	-	-	1	-	1	-	-	-	2	4
Desires pregnancy	-	-	36	1	7	4	14	6	4	72
Other non medical	2	-	1	4	3	1	1	-	5	17
One explulsion	-	-	2	1	2	-	-	-	8	13
Loss of followup	-	-	2	1	2	-	-	-	10	15
All reasons	10	3	120	48	169	10	26	7	309	702
%	1.4	0.4	17.1	6.8	24.1	1.4	3.7	0.1	44.0	

Apart from bleeding abortions which are being taken seriously and treated as the prmary reason for the large discontinuation rates. Other factors like other medical reasons (which I shall detail now) non medical factors, loss to followup etc. are seen as deterrents which can be overcome by better counselling motivation etc. If we compare the discontinuation rate we will find that uncertain factors like loss to followup account from 12.7 percent per 100 women and in one instance where the menstrual diary of 15 such subjects were analysed 10 of these loss to followup subjects had "acceptable" patterns of bleeding and only 5 were in the "unacceptable" pattern.

In the category of other medical reasons vaginal related reasons were pronounced.

Cumulative discontinuation rates for vaginal related reasons.

Discontinuation reason		months 3	6	9	12
Discharge	rate	1.0	2.0	3.0	3.5
	N	9	16	22	25
Irritation	R	0.9	1.0	1.2	1.2
	N	8	9	10	10
Infection	R	0.3	0.7	1.2	1.4
	N	3	6	9	10

Similarly other factors like pain, dyspareunia, odour, nausea, dizziness, palpitations and bowel pain all played a role in case where there was removal of rings.

Cumulative discontinuation rates for non medical reasons and loss to followup.

Discontinuation reason		Months			
		3	6	9	12
Partners ~~Patients~~ request	R	1.3	1.7	2.0	2.2
	N	11	14	16	17
Wish to become pregnant	R	0.4	1.1	2.7	3.8
	N	3	6	18	24
Other non medical reasons (This could range from curiosity, to clean to show husband, vaginal douche, unknown by mistake)	R	1.4	2.3	3.6	5.2
	N	12	19	27	36
Loss to followup	R	4.5	7.5	10.2	12.7
	N	40	64	83	99

So it is obvious that a combination of factors have led to the high discontinuation rate of 50%. But according to this report on the trial - this specific clinical trial showed a low rate of reporting for trivial vaginal irritation and discharge. Therefore from a clinical point of view these minor side effects appear to be of little relevance.

Adverse Reaction:-

Two discontinuations occurred due to adverse reactions caused by the use of ~~xx~~ progesterone releasing ring. In the first case the subject became hypersensitive after six months of ring use and following removal the blood pressure returned to normal. In the second, the subject discontinued at day 56 complaining of generalised itching and breast tenderness.

Hormonal Contraception - New long acting methods - Injectables & Implants - K No.3 March - April 1987. — Population Report

The synthetic hormones used in both injectables were developed in the 1950's. The progestin Medroxy progesterone acetate (MPA) the hormone in DMPA is derived from the natural hormone progesterone. DMPA is prepared in a microcrystalline suspension. Thus the hormone is not absorbed immediately after an injection. The usual dose of DMPA is 150 mg every 3 months. 6 month regimens of 250 to 450 mg DMPA are less widely used. The progestin Net-EN is derived from testosterone. Net-EN is prepared in an oily solution.

There are few known contraindications to the progestin only injectables. WHO recommends that women should not use injectables if they are pregnant, have cancer of the breast or genital tract or have abnormal uterine bleeding. WHO advises that women with history of diabetes or during pregnancy should be followed carefully since some laboratory tests have shown that DMPA alters carbohydrate metabolism

(WHO - Injectable hormonal contraceptives - technical & safety aspects, Geneva, WHO, 1982 - WHO publication No.65 - P.45)

On menstrual changes - (Population Report states)

Amenorrhea most common and occurs more often with the DMPA. In the 1st year 55% of DMPA users do not menstruate for 90 days or more compared with about 30% of Net-EN users.

very heavy or prolonged bleeding, a potential health threat is uncommon. In a WHO multicenter trial only 1200 women needed treatment for heavy bleeding - in almost 14,000 women months of

Similarly in a 12 month field trial in Pakistan only one of 2,147 women required curettage for prolonged bleeding.

Generally amenorrhea and light bleeding/spotting do not require any special medical treatment. Most family planning providers find that they can allay women's concern by counselling them before an injection and reassuring them if menstrual changes occur.[1] Oral contraceptives or supplemental estrogens to regularize menstrual bleeding are not presently routinely prescribed. For heavy bleeding WHO recommends either (1) one combined oral contraceptives daily for 14 days or (2) an inter muscular injection of a synthetic estrogen - 5 mg estradiol cypionate or estradiol valerate.

But most women stop using injectables because of menstrual disturbances than for any other reasons. In recent trials 9 to 30% of women discontinued the method in the first year because of changes in the bleeding pattern.

Perhaps because of different cultural and religious attitudes towards menstrual disturbances or because of the varying availability of counselling and follow up.

On Reproductive Effect:-

In Thailand because of fears that DMPA might cause permanent infertility the national family planning programme do not allow women to use DMPA unless they have at least one child.

Experience with injectable contraceptives in Thailand - British Journal of Family Planning - 6 -14 January 1987.)
A median time to conceive after a DMPA injection was 9 months or 5½

1. Gynaecologists admit that counselling is very difficult in the case of amenorrhoea. Women fear pregnancy - as cause of sterility - And short of giving estrogen there is no way to regulate it.

months after the end of the presumed duration of effectiveness. Despite this initial delay over 60% of former DMPA users because pregnant within 12 months and over 90% within 24 months. become

With NET-EN return of fertility can also be delayed. In a recent study of 89 women who stopped using NET-EN to become pregnant and who were followed for a year average time to conception was longer than among 92 former T Cu-200 IUD users. After one year - 73% of former NET-EN users had conceived. (ICMR - Task Force on Hormonal contraception - Return of fertility following discontinuation of an injectable contraceptive - Norethisteron denanthate (NET-EN) 200 mg dose - contraception 34(6) 573-582 - December 1986)

Data based on 9 Indian women therefore a spacing method not appropriate recommend to the users.

On harmful effects on children exposed to injected progestin contraceptives either in utero or during breast feeding. Several studies in the 1970's reported no increase in birth defect or prematurity when pregnant women were inadvertently given contraceptive doses of injectable progestins (One of these studies was conducted by Upjohn Company - Depo Provera for contraception; Information for PublicBoard of Inquiry on Depo Provera; responses to the Board's questions - submitted to the US, FDA, Public Board of Inquiry - UpJohn Company 25 June 1982 - P 155)

But in a recent study of Thai children by Tieng Pardthaisong and colleagues, however children of former users of DMPA were two times more likely to have peripheral limb defects and about five times more likely to have chromosomal abnormalities then children of women who used no contraception.

[Chandacham A, Pardthaisong T, Gray R, McDaniel E.B —

Contraceptive use and pregnancy outcome in Chiang Mai, Northern Thailand, 1986 (un published) yet another study is being conducted in Israel - Preliminary analysis from a study in Israel involving nearly 200 adolescents who were exposed in utero to (MPA) and over 950 controls found no evidence of retarded or precocious development or any disturbance in sexual development, sexual behaviour or growth among those exposed. But these studies on Thailand and Israel supported by WHO and Family Health International are continuing to look at children exposed in ~~xxx~~ utero to DMPA, MPA or oral contraceptives. (WHO special programme on R, D & T in HR - Thirteenth Annual Report, 1984, Geneva, December 1984 (152 p)

The very small amount of hormone transmitted in breast milk appears to have no effects on children even when followed upto 10 years.

Unlike oral contraceptives that contain estrogen. DMPA and NET-EN appears to have little effect on the cardio vascular system. There has been very few reports of blood clots or other cardiovascular complications in women using injectables. But adequate epidemiological studies have not yet been conducted.

Effects on lipid metabolism are less clear since long term studies are not finished. A few studies report an increase with cholestrol with longer use of DMPA (Lie ~~w~~ DFM NG, CSA, Yong, Y M & Ratnam SS, Long term effects of Depo Provera on Carbohydrate and lipid metabolism - Contraception 31(1) - 31-54 January 1985) Also reported is a decrease in high density lipoproteins ~~a decrease in high density lipoproteins~~ (HDL) both possibly adverse effects (Kandeel K M , Nayel, SA and Abeza MS, The effect of injectable contraceptives on lipid metabolism in women. Biomedica Biochimica Acta - 43(1) 111-115, 1984 Kremer J , De Bruijn, HWA and Minkiks F.I, Serum high density lips proteins cholestrol levels in women using a contraceptive injection of depot- Medroxy progesterone

Acetate - Contraception 22(4) 359-367 - October 1980) The only study involving NET-EN also found a decrease in HDL (For Hershy

M- Traynor I, Howard G, Hamawi A and Elder MG - Effect of injectable Norethersterone Oenanthate (Norigest) on blood lipid levels - Contraception 25(4) 435-46 - April 1982) Because NET-EN is a chemical similar to testosterone it is likely that it would reduce HDL levels slightly. Whether the small decreases in HDL sometimes seen in women using injectables have any clinical importance is not certain. WHO trials are underway in five countries to measure lipid metabolism in women using DMPA and NET-EN for short and long periods.[1] (WHO special programme of R, D & T in HR, Fourteenth Annual Report, 1985, Geneva WHO, December 1985 - 216 p)

CANCER - Major contraversy about long-acting injectables are whether they cause cancer? Main reason why DMPA has not been approved for contraceptive use in the US. Two species of laboratory animals - beagle dogs & rhesus monkeys given large doses of DMPA or NET-EN for long periods have developed benign and malignant tumours of the breast or endometrium (lining of the uterus (UP John Report and WHO facts about injectable contraceptives 1982) But until recently human studies limited.

WHO conducted a case-control study involving over 1,500 cases and over 5,800 controls in Kenya, Mexico & Thailand. The US centers for Disease Control and other organizations conducted a smaller study in Costa Rica involving over 700 women with breast cancer, invasive, cervical cancer or cervical carcimonia in situ and over 760 controls. Like other epidemiological and clinical research in the US, Canada and Thailand, the WHO case control study found no link between DMPA use and cancer of the breast, endometrium, ovary or liver (Memorandum from WHO 1986).

1. The effect of injectables on lipid metabolism is a cause of concern to gynaecologists

But the Costa Rican study found a two fold greater risk of breast cancer among former DMPA users than among non-users a statistically significant increase. But researches regard these results as inconclusive however as the number of cases is small. Only 19 women with breast cancer had ever used DMPA. Furthermore there is no indication that the risk increased with the duration of use. (Lee N C, Rosero L, Oberle M W, Grimaldo C, Whaterly A, Rovira E DMPA use in costa Rica and the risk of breast cancer (abstract) presented at the 114th annual meeting of the American Public Health Association, Las Vegas, Nevada, September 28-October 2, 1986.

In the WHO study the risk of invasive cervical cancer appeared to be slightly higher for former DMPA users than for controls. The study found that women younger than 36 who had used DMPA for more than four years were two times more likely to develop cervical cancer than controls younger than 36. But interpreting this finding is difficult because the number of cases is small. But the Costa Rican study found no increased risk of either invasive cervical cancer or cervical carcinomia is situ and among former DMPA users of any age or with any duration of use (Oberle M W, Irwin K, Fortney J Rosero L. Cervical Cancer and hormonal contraceptive use in Costa Rica (Abstract) presented at the 114th Annual Meeting of the American Public Health Association Las Vegas Nevada, September, 28 - October 2, 1986.

Tests Underway on New Long Acting Ester Injectables:-

A 12 year collaboration between the WHO and the (US NICHD) and scientists throughout the world has led to several new injectable compounds that may prevent pgegnancy for two or three months.

In 1975 WHO convened a group of chemists and biologists to begin the development of a new contraceptive steroids. Research focussed

on two progestins. Norethindrone and Levonorgestral and scientists synthesized over 230 esters derived from Net or Levonorgestral (an ester is a combination of steroid and an acid) US NICHD then tested these compounds in animals. Four compounds all derived from Levonorgestral were selected for further testing because they consistently inhibited ovulation in animals and appeared to be long acting.

Trials with one compound designated HRP002 suggest that a 20 mg dose will prevent ovulation for three months. Preliminary effectiveness trial planned to begin in 1987. Second compound HRP011 chemically similar to another progestin, norgestimate that does not cause marked endometrial or menstrual changes in animals. NICHD plans to begin small effectiveness trials of HRP011 in women which will determine whether it will have less effect on bleeding patterns than DMPA and NET-EN. Initial studies of HRP011 in a small number of women in the US are being planned for late 1987.

Advantages - The chemical properties of esters the new injectables are released from the injection site at a fairly constant rate without the initial high release that occurs with DMPA & NET-EN. These injectables can be administered in a simple aqueous microcrystalline suspension like that used for DMPA. They can be manufactured easily and inexpensively. Like DMPA and NET-EN administered with a simple injection which any health worker can administer without special training.

RU 486 ?

A steroid derivative synthesized by Roussel Company is being increasingly used in France to regulate human fertility and it acts by competing with progesterone at the receptor level. The contragestational or early abortifacient activity during early and mid pregnancy could involve interference with the decidualized endometrium. RU 486 has now been shown to influence the placenta as assessed by its effect on cell cultures from human placenta. The addition of RU 486 decreased the production of ECG, hCL and progesterone by these cells under culture.

There are three anti-progestins RU 486 (Mife prestone) ZK 98.736 (lilo pristone) and ZK 98.299 which have been studied in some detail but only RU 486 has been tested clinically on a wide scale. The first clinical trial of RU 486 was conducted in France in 1982. The initial trial by the WHO was a dose finding given twice daily for four days to a group of women in early pregnancy. All but 3 of the 36 women with intra uterine pregnancy started to bleed during RU 486 administration. In subsequent investigations a variety of treatment regimens were employed to improve efficacy ... It was also found that by the efficacy analogue, Sulprostone invariably after RU 486 administering synthetic prostaglandin was raised to 95%. Similar results were got by a vaginal administration of another prostaglandin gemeprost i.e. immediately after treatment with RU 486.

In defence of RU 486 in the third world. Specifically India.

Dr. Banoo Coyagi, Director of K.E.M. Hospital, Pune.

Defends RU 486 on the plea that there is a basic acceptability of such methods in rural India. Quotes a particular incident to support it. "..... a women's meeting was in progress in Pimpale Jagdat a small village of the Vadu Rural Health project of the K.E.M. Hospital, Pune, Maharashtra. Into that small room walked Professor Sune Bergstrom the Nobel Laureate and father of Prostaglandins accompanied by the project staff ..... the Professor hesitatingly asked them if they had delayed periods would they use pills to bring on menstruation ? At once they put out their hands for the pills. Although he advised them to go home, talk to their husbands and then make their decision, the community health worker stood up and said that it was not necessary ..... "There are three women in their room who have missed their periods they want the pills". This spontaneous response to a male foreigner by illiterate village women revealed more succintly to him than any research project the need and acceptability of such a pill in India.....".

Three-quarters of Third World Women live in countries where abortion is legal at least on health grounds. Take the example of India where abortion has been permitted since 1972 for a ~~board~~ broad range of health reasons including contraceptive failure. Yet in 1982 compared to an estimated 3,76,000 of legal abortion were four to six million abortions performed outside approved facilities. Accordingly to Dr. Banoo Coyagi what is paradoxical is that while million of women die of abortion services-with increase

in the 1990's given at 25 % increas in the number of women aged 15 - 24 - a safe and well researched drug like RU - 486 has cause a rumpus between drug manufacturers, politicians, bureacrafts and women's groups.

RU - 486 or Mifepristone it is argued is extremely effective in inducing ~~in-ducing~~ early abortions when associated with prostaglandins. Apart from being safer and more effective.

- It can be used in relative privacy
- is more acceptable culturally
- can be used on an outpatient basis by trained para medics only backed up by medical personnel and no need for facilities like - theatres and anaesthetics which are in such short supply.

Does it not have to be performed within 15 days -

Most of the research on Mife pristrone and allied drugs has been done so far in the first world by WHO's special programme Human Reproduction and Researchers in France, Sweden, Hungary and Britain. Some trials have been carried out in China and are now starting in K.E.M. Hospital Pune. my hospital. There are many questions that needs answers, the minimal optimal dose, the interval between RU 486 and prostaglandins the safety and efficacy in anaemic women, the acceptability, the logistics and so on.

Other questions that third World Government will need to ~~be~~ answered are public sector costs. Supply on the large scale required and the transfer of technology. Some facts about RU 486 & India. Around end of October ICMR will begin conducting

clinical trials on RU 486 on a test sample of 200 urban Indian women. The three pills - amounting to a dose of 600 mgs of RU 486 will in reality induce a "chemical miscarriage" by discouraging the fertilized egg from fastening on to the wall of the womb. In 80 out of the 100 women tested in France the embryo was expelled through what was the equavalent of heavy menstrual bleeding. But if its efficacy needs to be increased to be 96 % it needs to be combined with a dose of prostaglandins in injectable or pessary form. With the help of prostaglandins the incidence of heavy bleeding occurring with Mifepristone is reduced. In fact the company - Roussel UCLAF is very sceptical about the use of RU - 486 in the Third World. Roussels's Head of clinical Research Dr. Andre Ullmann who was closely associated with the drug's development stated bluntly that there was no possibility of using RU - 486 as it is used in France in a developing country setting. The synthetic prostaglandins. necessary (whether injections or pessaries) require a freezer chain (-20oC) although room temparature prostaglandins are currently under development. If I were Minister of Health in a developing country, I would prefer to spend my money on training nurses in vacuum aspiration.....

So in India to circumvent this difficulty a vaginal route suppository will be used. The attempt is to evolve a single day administration of the pill, together with a delayed acting prostaglandins. Moreover in India during the trials the women will be administered only a third of the dose that is, normally prescribed abroad that is 200 Mg as ICMR studies also aware that a lower dose will be equally effective -

ICMR is also aware that

that this kind of abortion is not a simple "do it yourself method. It will require close medical supervision especially as it can only be used only till the seventh week of pregnancy thus making it imperative to pin point the exact date of conception. In France the women must sign a form agreeing to an aspiration in case of method failure. So, obviously this has to be monitored carefully. What about cases where RU 486 causes severe bleeding. One French women said after using the method "A long process which requires time and supportive clinic staff and which is exhausting, like vacuum aspiration (which I have also had) ....." Given the average Indian women's anaemic condition the side effects of heavy bleeding can be dangerous. Dr. Saxena assures that the "clinical trials will look into the problem of effects on Indian women (as opposed to French women) based on pharmogenetic differences".

Institute for Research in Reproduction (ICMR) Bombay, India and Schering AG, West Berlin.

Effects of Progesterone Antagonist ZK 98299 on Early pregnancy and Foetal outcome in Bonnet Monkeys.

ZK 98.299 (Onapristone) is a progesterone and gluco cortécoid corticoid antagonist like RU 486 its preferential target calls are those of the endometrium and decidua

The study demonstrates that ZK 98.299 at the dose regimen used terminates early pregnancy in 62% of animals. Since in the three cases in which treatment tailed ZK 98.299 induced a decease in progesterone levels and in two of the animals transient episodes of vaginal bleeding it is possible that an increase in the dose or frequency of administration might improve the abortifacient efficacy.

But what is important to note that in the failure the pregnancy did not continued unaffected. The decease in the circulating progesterone levels after treatment, the presence of haematoma and blood clots in the placental tissue and the retarded foetal growth suggest that the treatment disrupted at least partially the conceptus. However the induced uterine activity was not sufficient enough to expel it. Therefore given the fact that if the treatment fails and the pregnancy continues the foetus is exposed to the risk of malformation.

RU 486 has been tested clinically for termination of early pregnancy on a wide scale and its abortifacient efficacy is between 60 to 80% depending upon the duration of amenorrhoea and dose and frequency of administration. But its clinical efficacy is

lower than prostaglandins. Moreover there is no information on the foeto-toxicity and foetal outcome in RU 486 treated failures. Therefore it is essential that in such cases pregnancy is terminated by alternate methods as these drugs at present have teratogenic effect. Moreover it is not clear why ZK 98.299 treatment to monkeys and RU 486 to women does not induce abortions in all cases.

Since ZK 98.299 induced vaginal bleeding in most of the animals and similarly in RU 486 treated cases most of the women start to bleed during the treatment period it appears that the insufficient release of prostglandins might be the plausible cause of failure to expel the conceptus.

WH 3.36

Serious risks and the risk of the malformation to the Foetus it is being tried by ICMR -

Attached to this is an interview by Dr Banoo Coyaji, K.E.M. Hospital, Pune one of the centers of the Human trial Annual Trial Data on ZK-98.299 of Institute for Research in Reproduction (Bombay

RU-486 - ZK-98.299:
are all ~~anti~~ abortifacients
which could bring about
chemical abortions - The ~~trial~~
human trials are about to
begin - and these drugs are
seen as a potential back
up method for future
Family Planning Programmes - And despite
all its hazards and unknowns

(1)

RU 486 - The French Experience.

RU 486 is now fully licensed in France where it ordered and used by hospitals and licensed abortion clinic. Bears the trade name Mifegyne. Its use is so tightly controlled that each box is numbered and must be accounted for. Mifepristone - The geneic name for the drug is an antiprogestin which renders progesterone, ~~the~~ ~~hormone~~

the hormone secreted during the second part of a women's menstrual cycle inert has three main effects when given in the early part of pregnancy.

It causes the lining of the uterus to break down as it does during a menstrual period and the implanted egg is lost with the timing. It causes the uterus to contract. It dilates the cervix. If the appropriated dose is taken up to 41 days of amenorrhoea (since the beginning of the last period) and if the dose is followed 48 hours later by a prostaglandin in injectable or pessary ~~pessey~~ form the efficiency increases.

But what is interesting and significant is the complicated French procedure for conducting an RU 486 abortion in France.

After ~~nursing~~ missing her period the women must visit her doctor and ask for BHCG blood test and an official request for an abortion. This visit must effectively take place within 2 weeks of the nursed period because under French Law there is a "cooling off" period of five days between requesting an abortion and having the abortion . Mifepristone can only be taken up to the 49th day of amenorrhoea. An appointment must then be made at a suitable hospital or clinic. The women must take the results of her blood test and the doctor's letter to the clinic undergoing an ultrasound examination to check the gestation of the foetus and to the ensure that the pregnancy is not ectopic be questioned for possible counter indications (eg. Asthama, cardio vascular problem, allergies and women over 35 who ~~spoke~~ smoke) sign a form agreeing to an aspiration in case of method failure and finally swallow three 200 mg mifepristone pills. Two days later return the clinic to receive an injection of prostaglandin and stay there

for three or four hour until pains and contraction have ceased. Ten to fifteen days later must return for a compulsory check up with either a ultrasound examination or BHCG blood test to ensure that the abortion has been completed.

Despite some obvious advantages in that no hospital beds, anaesthesia or surgery not all gynaecologists and hospitals are using it widely because it is rather complicated for hospital administrators to manage. The gynaecologists may have less of a role but nurses and other paramedical staff must be involved and well trained. From the health point of view infections have not entirely disappeared fragments can be retained and cause infection but traumatic complications of surgery perforations of the uterus and scarring have vanished.

Roussel Uclaf. not ~~beer~~ keen on launching the drug in the United States. Possibility of confrontation with antiabortionists problems of liability and distribution ~~xxx~~ peculiar to the U.S. Next country to apply for product licence is likely to be the U K where extensive trials have taken place followed by Scandinavian countries and Belgium.

DEVELOPMENT OF THE ANTI-hCG VACCINE

The two major questions regarding the safety and efficacy of the vaccine are: (1) Could an anti-hCG vaccine break material tolerance to the hormone and elicit an immune response of sufficient magnitude to neutralize the hormone in the ~~material~~ circulation at the peri-implantation stage of "gestation".

2) Could an anti-hCG response so produced be restricted to the intended target so that cross ~~sections~~ with other normal body constituents particularly endogamous pituatory hormone ~~(anti)~~ would not occur and endocrine and metabolic disturbances and the potential risk of immunopathology avoided.

Phase I clinical evaluation of the Ist generation anti-hCG vaccine.

Ist generation anti-hCG is a synthetic peptide representing the B-hCG carboxy terminal 109-145 peptide (B-hCG CTP) coupled to the diphtheria toxoid carrier (DT) molecule mixed with a muramyl dipeptide (MDP) adjuvant and suspended in a squalene arlacel - saline emulsion vehicle.

Objective of Phase I clinical trial to determine what, if any, side effects were produced by this vaccine. Also to measure and compare the levels of anti-hCG antibodies elicited by the vaccine.

30 previously sterilized women volunteers were recruited. Six of the 30 women volunteers were assigned to each of the five dose groups. The highest of which, group being the dose expected to elicit a level of immunity. Sufficient to confer anti-fertility efficacy of the six women in each dose group four received the complete vaccine and two received a "placebo" preparation consisting of the MDP adjuvant and emulsion vehicle only. Immunization was effected by two injections into the gluteal muscles at an interval of six weeks and the subjects were followed up on an in-patient and out-patient basis for a total of six months.

Majority of vaccine recipients in all dose groups produced comparable anti-bodies to hCG as well as to the DT carrier ~~compensate~~ of the ~~vaccine~~. The only side effects considered significant by the resident physicians were transient muscle and ~~gut~~ pains joint reported by a few subjects.

So far as the Phase I clinical trial is concerned the primary objective has been successfully achieved in that the desired type of immunity has been elicited in most of the vaccine recipients without the production of unacceptable side effects.

Given this success it was proposed that the next stage was a limited study with the B-hCG CTP vaccine formulation in a small number of fertile women volunteers to determine if anti-hCG antibody levels in excess of 05 nanomoles of hCG binding capacity will provide an anti fertility effect. But before seeking approval to conduct this study in women animal experiments will have to be conducted to determine if any fetal abnormalities are associated with the vaccine's use.

Protocols for animal experiments and for the clinical study have been conducted in consultation with Task Force scientists and clinicians and with representatives of the pharmaceutical industry and national drug regulatory authorities.

Valuable additional information has been obtained in the phase I clinical trial relevant to the development of a safe, effective and acceptable anti-hCG vaccine suitable for wide scale application particularly in the developing countries.

Defects in this system: In the current formulation the long peptide is more expensive and difficult to manufacture and characterize so future vaccine production would be greatly facilitated if one or more short peptides of B-hCG could be identified.

Out of total of approximately 80 injections with the B-hCG CTP vaccine that were made during the course of the trial, adverse reactions to the DT component were seen in two instances. Whilst this may appear to be a very low incidence it would probably be regarded as an unacceptably high level when large scale use of the vaccine is considered.

To limit the MDP dose and improve on the vaccine delivery systems are necessary.

The complex and viscous emulsion used as a vehicle for the current vaccine is obviously not suitable for use beyond the preliminary stages of clinical testing.

Future Directions

The Task Force is proposing to carry out the following activities during the 1988/89 biennium.

Subject to a satisfactory outcome of animal teratology studies approval will be sought to carry out a limited efficacy evaluation of the current anti-hCG vaccine formulation in fertile women volunteers. Also aim to develop an improved version of this vaccine using a slow release delivery system designed to elicit long lasting immunity from single course of immunisation as well as the development of a second generation of anti-hCG vaccine that will represent a viable product prototype.

Anti-sperm vaccines and to evaluate prototype anti-trophoblast vaccine are other areas of study of the Task Force.

A Meeting on vaccine safety in order to develop guidelines for preclinical & clinical safety evaluation of vaccines in general and for anti-fertility vaccines in particuler will be convened by the Task Force.

The Task Force steering Committee meetings include representatives of CONRAD, the Population Council, The Indian National Institute of Immunology and the US National Institute of Child Health & Human Development.

International Experience with Norplant & Norplant - 2 Contraceptives.
Irving Sivin
Studies in Family Planning - Vol. 19 - No.2 - 81 - 94 (1988)

Menstrual Problems & Pattern change with time.

Alterations in periodicity of the menstrual cycle, changes in the duration volume of menstrual flow and spotting are the most pervasive side effects of implant contraception. In initial and subsequent studies few women have terminated implant use because of amenorrhoea or oligomenorrhea but termination of use attributed to menorrhagia or metrorrhagia (i.e. heavy bleeding) have been more frequent.

There have been instances in which vaginal bleeding has been extremely severe. One woman among 3,700 implant acceptors monitored by the Population Council recorded uneventual use of Norplant - 2 rods for several months and then suddenly experienced very heavy vaginal bleeding accompanied by a precipitous drop in her haemoglobin levels. The rods were removed, she was transfered and had an uneventful recovery. Two steep falls in haemoglobin levels have been reported among the first 12,000 implant users in China.

Medical Problems Unrelated to Menstruation.

On the basis of the data for the "three country" study which involves Chile, Dominican Republic & Finland and single country trials from the Dominican Republic, United States & China it was felt that with the exception of China all the countries registered between half (51.0%) and 2/3rds (64.3%) of all terminations were attributed to symptomatic complaints rather than to well defined diseases. In contrast in the People's Republic of China, subjective complaints accounted for between one fifth (21.1%) Norplant - 2 to one-third

(33.1%) Norplant) of all medical terminations.

Headache one of the pronounced reason or symptom that led to removal. In the U.S. between 19 (Norplant) and 25 (Norplant - 2) per cent of medically related terminations were attributed to headache. In the three country study about 21% opted out due to headache. In China also although headache was the most frequent cause of termination among Norplant capsule users it accounted for only 11%. Complaints about weight changes both increases and decreases were also common. Americans terminated largely due to w weight gain (19.3) the Dominican women by a ratio or 14 to 4 were more disturbed by weight loss, Mood changes, anxiety, nervousness and depression were also associated with the use of the method. The remaining symptoms and complaints that led to termination are diverse in nature; among the most frequent have been vertigo, nausea, nusculoskeletal pain and abdominal pain.

But unlike American where circulatory and cardiovascular problems leading to termination were infrequent i.e. the American figures were 1.8 and 5.4% of all medical terminations for Norplant and Norplant - 2 respectively.

2. China these factors played a major role. In China cardiovascular and circulatory problems represented 11.2% medically related terminations of Norplant use and 28.9 per cent of these terminations from Norplant - 2 use. Mild hypertension and heart rate problem were the most common of these conditions. A few cases were diagnosed as myocarditis.

Similarly in the three country study mild hypertension was the single diagnosis reported in this category of medical terminations. Although anaemia was not common it did happen to one woman in

California and two Chinese women. But Chinese physicians also reported a number of cases of low platelet counts during implant use including one of primary and one of chronic thrombo cytopenia.

Endocrine problemsreported in the Dominican Republic and in China for Norplant capsules were primarily thyroid problems. In China in addition to hyperthyroidism one case of pituitary tumour was reported.

Skin problems resulting in removals were rashes, dermatitis and acne. One case of breast cancer discovered in the first year of use led to removal of rod implants in U.S. The other breast related removal was mastalgia (pain in the breast) which occurred in two women.

Terminations because of pelvic related conditions focus on a few problems, like functional ovarian cysts, uterine fibroids or myoma and lower abdominal pain. Another complication observed in the three country study was Hot two Norplant capsule acceptors had epileptic seizures as some drugs used in the treatment of epilepsy counteract the contraceptive effect of levonorgestrel.

Despite all this adverse data

It was concluded that all this data from various implant studies "represents prima-facie evidence that Norplant implant do not present major health concern to users." Given the efficacy of the implants in preventing pregnancy the ensuing health benefits are likely to outweigh by far the risks of Norplant Contraception".

OFFICIAL REPORT ON CONTRACEPTIVE TECHNOLOGY- AN OFFICIAL OVERVIEW/ STATUS REPORT.

CONTRACEPTIVE TECHNOLOGY PAST - PRESENT & FUTURE - STATUS

REPORTS SERIES — N I H F W

WH 3·389

I. NIHFW - Dr. R.P. Das Associate Professor, Department of Reproductive Bio medicine, National Institute of Health and Family Welfare, New Delhi - 1989.

Contraceptives of today and tomorrow. Field of population control emerging as one of prime importance in bio-medical research.

A variety of progestogens and ~~continuation~~ combination of progestogens and estrogens have now been used as injectable preparations or as subdermal implants.

Two long acting injectables are widely available a depot medroxy progesterone acetate (DMPA - trade name Depo Provera, the Upjoha Company, USA) and Norethindrone Enanthate (NET-EN), trade name Noristerat Schering AG, West Germany) Both are highly effective spacing (reversible) methods - DMPA is approved for use in more than 90 countries and NET-EN in more than 40 (but not in India).

The long acting injectables abolish the cyclical release of LH and FSH probably by an action at the hypothalamic hypothalmic level as observed with combination of oral pills. However ICs seem to have less effect on over all bodily physiology eg. liver or thyroid function than do the oral pills.

No serious adverse reactions. Major side effect is on patterns of menstruation irregularity to amenorrhoea. The over all blood loss is reduced but occassionally there are episodes of heavy bleeding. Many women gain weight on DMPA or NET-EN.

Numerous studies have shown that the use of injectable steroids is associated with a slow return of fertility. The median time to conception is about 10 months after the last injection with fertility returning to 75% of women within 15 months and to 95% in 24 months.

No adverse effect on the amount and duration of lactation. Infants of DMPA and NET-EN treated mothers gained weight more rapidly than controls.

The greatest debate concerning the use of long acting steroids has revolved around possible carcinogenicity. In some studies a higher prevalence of abnormal cervical smears has been recorded in DMPA users but not in other. The prevalence rate declines with duration of use and there is no evidence of any change in the risk of invasive cervical concern. low

On the possible relationship between the continuous ~~use~~ levels of progestogens and incidence of breast ~~cancer~~ — Only two cancer cases of breast ~~concern~~ cancer among DMPA users reported.

Since 1980 regulatory agencies in Sweden, the U.K. France and West Germany have approved DMPA for contraception. Several national and international s scientific groups have also endorsed DMPA, including WHO, HRP & IPPF.

Monthly injectables - widely used in Latin, America and China. They contain an Oestrogen and progestin combined. WHO is currently supporting research on two new monthly injectables and conducting trials on them alongwith Family Health International in three countries. 1[illegible]

WH 3-340

ICMR (TASK FORCE ON HORMONAL CONTRACEPTION) (PHASE II)

Randomized comparative clinical Trial of ~~Norbet~~ Norplant (R) Six capsules with Norplant (R) - 2 (Two covered Rods) Subdermal Implant for Long Term Contraception. Report of a 24 month study.

Research Centres.

A.I.I.M.S., Safdarjung Hospital, Kasturba Hospital, New Delhi, Rama Krishna Mission, Seva Prathisthan Calcutta, ICMR, New Delhi.

The need for a highly effective reversible estrogen - free contraceptive method in which a single administration sufficient for several years need not be stressed. Subdermal implants offers the possibility of a long-term contraceptive without frequent medical intervention or continual attention by the user. As a result of several years of research by the Population Council, New York the Norplant (R) contraceptive system has been developed which embodies several of the desirable features of a long-acting reversible fertility regulating method.

The ICMR (New Delhi) which actively collaborates in contraception research with International Committee for Contraception Research (ICCR) of the Population Council, New York initiated a phase II randomized clinical trial comparing Norplant (R)-2 with Norplant (R) in August 1982 at 4 of its Human Reproduction Research Centres. The present report summarizes the results of this study upto 24 months of use of these implants.

For the trial of the implants, Norplant (R) - 2, and Norplant (R) provided by the Population Council, New York based on the hormone levonorgestrel a total of ~~172~~ 172 subjects were enrolled in the study, while 84 subjects were allocated to Norplant (R) - 2, 88 were allocated to Norplant (R), The subjects were observed for 1590 & 1777 months of use respectively.

A total of 8 subjects, 5 with Norplant (R) - 2 and 3 with Norplant (R) had expelled one of the rods or capsules . Analysis of the menstrual pattern indicated that the proportion of subjects with menstrual irregularities continued to be high (more than 60%) throughout the study. Since menstrual irregularities were mainly excessive or prolonged or irregular bleeding only 20 per 100 users discontinued the method at the end of 24 months. This is unlike the observations made in connection with another clinical trial with NET-EN (200 Mg) given as either two or three monthly intermuscular inject ion in which 42 per 100 users had discontinued the method due to bleeding problems at 24 months of use.

Oligomenorrhoea

Thus it appears that an ~~oligoamenorrhoeic~~ menstrual pattern is more acceptable to thestudy propulation and discontinuation was more due to amenorrhoea. In fact 47 % of the subject had cycle length of more than 35 days with both the devices during the Ist reference period The figure continued to be high (i.e. aoout 55 %) until the 8th reference period. The above

observation indicates that the majority of women using norplant devices experienced oligomenorrhoea. As result of the success of these trials the ICMR has recently initiated a phase III multicentre clinical trial with Norplant (R)-2 to confirm the observations of this study.

Insertion and removal of Norplant Implants require a minor surgical procedure under local anaesthetic and a small incision. Removal is more difficult than insertion. Although the status report of W.I.H.F.W. claims that infections are rare. Dr. Pramila ~~Seranayake~~, Medical Director of International Planning Parenthod Federation Points out that trained health workers are required to insert the capsulesin a clinical setting and the method is therefore not suited for community based programmes.

Dr. Somnath Roy, Director of W.I.H.F.W. admits that the hormone levenorgestrol while supressing ovulation can also cause ~~ac-ne~~, hair growth, weight gain, headache, nervousness and depression. Dr Roy also apprehended the possibilities of infection due to the ~~lack~~ of hygiene on the part of the paramedical staff. According to Dr Roy "Experience gained from the clinic based trials does not provide adequate guidelines and preparation for programme operation. This is absolutely true in cases of injectables and implants". In order to be successful "it would be important to make the technology suitable to the culture of the people and capability of the service system".

Although Dr. B.N. Saxena, deputy D.G. of ICMR and a coordinator for the Norplant trial ~~based~~ that it would change the whole complexion of contraceptive use in India" the women activists saw the menstrual irregularities the greatest impediment or the worst fall-out.

WH 3.41

Norplant - An account of its use in Bangladesh.

Bangladesh Fertility Research Programme (counterpart of ICMR) attempted to start Norplant trials in 1981. But due to resistance from various groups trial postponed by BFRP to February 1985. They were financially & technically assisted by the Population Council & Family Health International.

In an article by Dr. Halida Hanum Akhter the then Director of BFRP she openly acknowledged that, "It has been found by researchers that contraceptive pills containing progestin and more commonly used other reversible method necessitated continuous motivations involvement from by the user. In a country like Bangladesh this fact is more true than in the developed world. It is therefore necessary to introduce methods in Bangladesh which can continue to be effective for long periods without continuous motivation by Family Planning Workers. Norplant is perhaps the most effective method which is likely to prove successful here."

Again even before the BFRP undertook the trial in February 1985 the third Five Year Plan justified the use of Norplant on the grounds that this ".....longlasting method has the potential advantage of not requiring day to day use and therefore may be particularly suitable for our semi literate population ..... the programme for its wider use can be decided according to the experience of the trial. Here again the effectivity question is mentioned and is specially targetted towards the semi literate population, in other words the poorer section of the population so that population control can be assured".

(In these statement you have a blatant profession of the discriminatory principles of ~~eugenics~~ eugenics. Although the ICMR is wary of such indiscretions and in fact takes care to pose the issue with a"pro-women" bias explaining its rationale from their inner urges and needs, yet there is no doubt that the very basis of long acting contraception like injectables and implants etc is to prompt women from having control over these issues).

Critique about the "facts about an Implantable contraceptive" - Bulletin of the WHO -(1985)

1. Insufficient Animal experiments

(a) Levonorgestrol and the half actived I, Norgestrol Isomer was used interchangeably and therefore the interchangeable use of two substances is confusing.

Comparison of the doses given to animals and humans is misleading as there are big differences between species in terms of bioavailability and terminal half lives of the drugs.

3. On the one hand the beagle bitch is considered an unsuitable model for studying progestagins but experiment with this animal are included and no replacement experiments were carried out.

4. In the majority of the experiment Levonorgestrol was given by the oral route and comparison with implanted doses is misleading due to difference in bioavailability.

5. Rat which is a poor model for testing of implants is used in animal experiments.

Areas of insufficient Clinical Research.

1. Effect of Norplant on lipid metabolism experiments carried out are contradictory. And fat metabolism is associated with risk of cardiac problems.

2. Relationship between Norplant use and an abnormal glucose tolerance test (According to WHO only six examined in this connection.)

3. Safety of long term use of Norplant.

4. Effect of Norplant on blood coagulation.

5. Use of Norplant during lactation and its effect on the growth and development of the child.

6. Use of Norplant during pregnancy.

7. Its effect on the level of testosterone and nostenedione.

8. Its effect on systolic and diastolic blood pressure in the 4th and 5th years of use.

Inadequacies about the existing areas of investigation.

1. Women who had used injectable contraceptives were eliminated from this experimental series.

2. The results were often compared with those of women who use oral contraceptives and not with women who use no hormonal contraceptives.

3. In all the trials some of the side effects are not included in WHO reports. Very often more implants are removed for "other medical reasons" than for menstrual irregularities. In these categories are side effects like depression, drastic weight loss and epilepsy.

UBINIG raised many questions about the ethics of such research particularly the poorer sections who because of their vulnerable condition was in danger of becoming a victim of such research. It revealed the discrepancies in a publicity leaflet issued by the Institute of Post Graduate Medicine & Research (IPGMR).

"Norplant is a new temporary FP method -

Effective for five years

Its use is relatively easier

It is given under the skin of an aim with an injection needle

Its side effects are less than the pill 100% as effective as sterilization. The user can take Norplant whenever she wants.

Fertility will return after one year can carry out normal movement work when it is in the body. No need of taking any other method when it is mi in the body.

Doctors will examine the client before the method is adopted.

This is a mixture of gross overstatement and understatements.

It is not 100% effective. The ~~annual~~ annual pregnancy rate during the Ist five years ranged from 0.2 to 1.3. WHO records indicate a gross cumulative pregnancy rate at 5 years of 2.6 per 100 women years.

Nor is its use easy. It need a surgical approach.

They also did a profile of Norplants users. Economic status of 6 - very poor. Economic status of 4 - lower middle class.

Education - 6 out of 10 illiterate

Age - two (15-20) three (26-30) one (31-34) and four (over 35 years of age) and highest age found to 45. Upper age limit of Norplant users must be 40.

Health conditions after use of Norplant Total N = 10

1.	Amenorrhea	10 (All in different periods of time)
2.	Irregular menstruation	4
3.	Burning sensation	3
4.	Excessive bleeding, white discharge, body ache	2
5.	Tiredness	1

Also six out of 10 women were breast feeding out of which two women had a child below one year of age.

And many complaints were registered as to how the users have gone to the centre to express their problem but were given only 30 vitamin tablets or in some cases a prescription to buy medicine from outside. Only 3 women succeeded in convincing the centre to remove off the Norplant.

Indian Data - on Norplant Trials:-

Note:- only got data for the phase-II trial. But the ICMR has completed the entire protocol submitted its report to the Govt. of India. As stated by Dr. S N Saxena (ICMR) Norplant (R-2) (two covered rods) has been recommended for use on a clinical basis i.e. by a trained gynaecologist. It has also been suggested that from the point of view of economies of production the rods would be cheaper to manufacture and clinically easier to insert. Otherwise all other clinical and metabolic effects as well as bleeding patterns were similar in these two groups of women.

What is important about this trial data is its - concentration on its efficacy and as a fall out of this ~~the~~ its impact ~~of~~ on the menstrual cycle is given maximum importance. Even the menstrual irregularities which was high throughout the period of study (i.e. about 80%) was considered more in the context of continuation/ discontinuation rates and not as a serious gynaecological problem. Moreover in comparison with Net-EN since discontinuation rates were lower it was concluded that the nature of menstrual disturbances i.e. excessive, prolonged or irregular bleeding were more acceptable to the Indian women. And therefore it was amenorrhea or less bleeding which was more problematic. What is pertinent and necessary to ask is whether Indian women with their anaemic-prone conditions can risk methods which can lead to excessive, prolonged or frequent bleeding. And whether the intermittent spotting which 62 to 80% of the subjects experienced with both the devices is merely a physical inconveniences for women or a health risk. In fact one of issues (as stated earlier) by the US FDA committee was whether irregular bleeding could imply or lead to "endometrial cancer"

It was also realized that apart from a more "acceptable" bleeding pattern another factor which contributed to the higher continuation rates was the "inherent characteristic of the Norplant contraceptive method". The realisation that any discontinuation of the method would mean a repeat surgical procedure for its removal may have been a disincentive. It is here that the issue of the woman losing control over her own body or reproductive rights becomes crucial. It is not certain as what extent the official claim that the higher continuation rates due to better counselling and follow up is ~~xixak~~ valid. It is quite possible that in the guise of counselling there may have been professional refusal to remove or a veiled refusal to remove unless backed up by strong medical evidence. And it is here that the periodic motivation which played a crucial role in the steep fall in continuation rates of NET-EN injections.- was not necessary. All that the medical professionals had to do was to discourage removal.

There is a lot of data to substantiate these fears in Bangladesh where scores of women have testified that despite suffering from severe bleeding, itching in the vagina, and other unbearable side effects ~~s~~ the family planning workers, doctors etc. ~~are~~ were disinclined to remove it. They ~~are~~ were either evasive or in some instances bluntly refusing to remove it. In fact one of the justification given by ~~a~~ the doctors in Bangladesh for refusing to remove it is that it is such an expensive method equivalent to TK 2000 (US $ 55) that the women do not have the right to "talk about removal". "How dare they when such an expensive medicine is given free of cost to these women".

Negative EFFECTS OF NET-EN/DMPA/ or Injected Progestins:-

1. DMPA alters carbohydrate metabolism

2. No way to control menstrual irregularity except to prescribe supplemental estrogens which defeats the purpose of an estrogen free contraception.

3. Delay in return of fertility - some as late as 2 years.

4. Thei children of users of DMPA two time more prone to limb defects and five times more liable to have chromosomal abnormalities

5. Increase in cholestrol with longer use of DMPA.

6. Decrease in high density lipoprotein (Both DMPA and NET-EN)

7. Costa Rican study found two fold greater risk of breast cancer among former DMPA users.

8. Similarly WHO also found risk of invasive cervical cancer higher in the case of former DMPA users.

9. Following an injection of Net-En the serum zinc level in the system decreases significantly. As zinc is an essential component of blood platelets a reduction in the zinc level could mean abnormalities of the blood platelets - a symptom that is common among pill users. This is regarded as a potential risk to users.

10. Net-En reduced prothrombin activity (a substance present in the plasma and essential for clotting of blood. There is also a suspicion that Net-En affects the hepatocellular functions of the liver. Which means that women suffering from jaundice or other liver ailments should not use the injection.

11. One detremental feature of progestogen based contraceptives is the effect it has on lowering the body's resistance to infection termed as immuno suppresant effect. The Dutch Medical Bulletin writing about DMPA says. "Like all other progestogens DMPA has a slight immunosuppressive effects. Clinical effects of this has never been written about."

WHO also advises that the use of injectable contraceptives such as NET-EN should be avoided if at all possible among young adolescence women who have not yet had children but may wish to do so in the future and women over 40. WHO notes that (a) the consequences for sexual development of interrupting pituitary activity in the first few years of adolescence are not fully understood; (b) and neither has the effect of DMPA and NET-EN on the subsequent fertility of women who have not had children been studied carefully. So women who wish to have children have been advised to use another method of contraception.

Finally women over 40 are also cautioned against the use of such injectables.

In addition WHO lists several "special problems" where great care in the use of injectables should be taken.

These include (1) abnormal liver function or recent history of liver disease, history or evidence of cardiovascular disease, congental hypertripidaemia, diabetes mellitus or history of gestational diabetes.

In all these cases WHO recommends very careful monitoring.

In fact the checklist in as follows:-

Check the following by history and examination

	Yes	No
Above 40 years of age		
Above 35 years of age and heavy smoker		
Seizures		
Severe pain in the calves or thighs		
Symptomatic Varicose veins in the legs		
Severe chest pains		
Unusual shortness of breath after exertion		
Severe headaches and/or visual disturbances		
Lactation (For less than 6 months)		
Intermenstrual bleeding and/or bleeding after sexual intercourse		
Amenorrhoea		
Abnormally yellow skin, eyes		
Blood Pressure (above 140 mm HG Systolic? and/or 90 mm HG diastolic?		
Mass in the breast		
Swollen legs (oedema)		

Only if all the above are negative the woman may be given injectable contraceptives.

Are these guidelines observed in India?

In India the procedure for testing a drug is that it must have the approval of the Central Drug Controller, Govt. of India. For this approval an initial toxicology, safety and efficacy tests are made which in turn are reviewed by a panel of experts. Once found suitable after testing the drug it is released to certain medical institution for further research. Here the Institutional Ethical Committee which is made up of professionals representing medical legal and religious faculties must be involved in reviewing the

and Documentation which investigated about the procedure observed many were lapses - The Committee was only involved- Moreover given the serious limitation of normally protocols of the tests. It is here the Centre for Education But

The public health facilities ever the manner in which the trials were conducted so raised serious misgivings

before we examine the issue of trials - a debate should be encouraged on the more fundamental issue of medical experimentation. It is here that hawks like Dr. B N Saxena assume importance. "How can we advance in this field of population control without human experimentation and trials? Can we prescribe a drug on the basis of its efficacy data from another country? In fact given the wide difference in the metabolic impact of these hormonal drugs (many recent studies proved it) it is absolutely essential that we marshall our own data and therefore these trials are in the interest of our people".

Granted that such a need exists then why not recruit articulate, well informed literate volunteers who can not only extend informed consent but will also be vocal in exposing any misdeeds and negligence of the medical community and demanding a back up medical care? It would be professionally most honest if the medical community offered itself as volunteers for the trial. "Nobody will be prepared to tolerate side effects like spotting. It is most inconvenient and giving their lack of need for it. it is obvious that they will not fall a trap to the " " or Guinea Pigs needs of the medical community. "~~guinea pig~~" says Dr. Kamla Ganeshan (Senior Gynaecologist) "Then what about the poor people how do you justify their involvement in the trials?".

"They are desperate and many of them express a desire to be given an injection to solve their problem. And since all contraceptives ~~of~~ or for that matter drugs have side effects they are prepared to tolerate it". Moreover since like all Govt. doctors she belong to the "benefit outweigh risks" school of thought injectable are a regarded

boon to these women and hence these trials are ethical.
(It is this kind of argument which makes it imperative for women's groups to ensure that a far wider informed debate takes place because if these injectables are included in the family planning programme it is very likely that many sections of women may opt for them).

Another related but equally important issue is that the Thrid World population (again because of its objective need) are ideal research material for field trials especially since norms for such research are extremely rigid in the advanced countries and the people too well informed and articulate to permit any kind of misuse of trials. For instance in the Multi National Comparative Clinical Trial of long Acting Injectable Contraceptives - NET-EN given in two dosage regimens and DMPA the final report of which was published in 1983 we will find that out of 13 centres included for the trial, 9 were in developing countries and four in developed. Even in terms of the number of women recruited for the trial and women months used in the trial of each treatment group reveals this discriminatory attitude. In the case of DMPA No.of women recruits from developing countries were 1377 as against as 210 in the developed countries (of which 130 women volunteers belonged to Ljubljana (Yugoslavia). In terms of women months it was 13, 167 against 2, 383 in the developed countries. Similarly in the case of NET-EN (60 days) it was 690 women from developing countries as against 99 from developed countries and NET-EN (84 days) 693 from developing countries as against 103 from developed. Here again the majority of the women were recruited from Ljubljana (Yugoslavia). of the developed countries

There is no doubt that the research establishment collaborates quite willingly with the drug multinationals in conducting the trials. At present while the ICMR is launching the trials of Ru 486 - an anti progestin or a progesterone antagonist - a steroid synthesized by the French company Roussel - The Institute for Research in Reproduction (Bombay) is collaborating with Schering AG, West Berlin in conducting trials on Bonnet Monkeys with another anti progestin - ZK-98.2ff-But to return to the issue of trials as conducted in India and the question of informed consent it must be noted that in India the testing is done mainly in government run public hospitals and in rural areas where women are uneducated and from the low incomegroup. Although on the question of consent the doctors on the programme insisted that consent was sought before the injection was administered, it was more in the nature of informing or alluring them to adopt this new method of injectables, since the IUD does not suit them. But nowhere are they explicitly informed that they are a part of a trial in which the drug is being tested. As far as side effects are concerned, they are only told about menstrual irregularities (an effect which they cannot suppress) but otherwise none of the other dangers or risk are even mentioned.

The Doctors admitted that "the class of people are like that they won't understand. Educated people would understand that there is nothing wrong with a trial but not these ignorant people. If we told them it is a trial then no one would be willing to have an injection".

Even the routine and more serious clinical examinations to investigate the women's medical history for diseases, hypertensions

and bleeding problems were not conducted in the manner desired. According to CED report "During our visit we found that a women is asked if she has any problems. No specific questions like do you feel depressed, have headaches etc. are asked. The Doctor justified it on the grounds that if they went by the checklist the answer would be yes to everything. The woman on trial when spoken to, stated that they had no problems except irregular bleeding. But when probed they admitted that they had giddiness and headaches. Moreover during the Phase-III Net-En two monthly trials it was noticed that even simple guidelines of the ICMR that women who were breast feeding their child should not be recruited was not observed. Therefore considering the fact that the medical staff were unable to ~~eliminate~~ regulate or monitor such a simple but vital rule to prevent lactating women from joining the trials makes one very sceptical about whether the more serious contraindications ranging from liver or cardiovascular disease to abnormal uterine bleeding and breast and genital cancer were examined to the necessary extent and on the basis women precluded from the trial. What is known as the preliminary screening to eliminate high risk clients.

And while referring to lactating women WHO report (1982) admits that a breast fed infant of a mother on NET-EN would receive about 0.05% of the maternal dose over a two month's interval. This according to another report may prove very harmful as the brain is not fully developed and may be sensitive to hormones. In addition the immature liver and the consequent slower elimination may lead to a higher accumulation of hormone in the blood (War on Want, Norethisterone Enanthate, Dec. 1984 U.K.)

But apart from all the above medical lapses it was also noticed that there was no effort to keep track of the patients once the trial periods were over. The doctor felt that, "if there were any problems the woman would come back to us".

But besides the disregard exhibited by the medical and paramedical staff there are other problems related to the timely distribution, administering and storage of drugs. If the injection is not administered within five days of its due date the contraceptive efficacy is lost. Which implies that the paramedical staff must be sufficiently motivated to follow up each case of injection at the right time intervals. As far as the issue of storing and administering the drug safely is concerned, the health ministry's special guidelines states that the NET-EN being an oily viscous solution should be aspirated carefully in the syringe to ensure maximum use and prevent leakage and also that the vial containing the drug should be warmed before injection if it has been stored in low temperatures (Too much to expect from our over worked health centres and govt. hospitals) Vaccine deaths have occurred due to wrong administration of the drug, faulty storage and negligence. Therefore in the wake of many incidents some major tragedies with triple antigen polio etc., it is necessary to be wary of it. In fact the ICMR in its trial report stated that "as the leakage of the drug" may be a "factor responsible for the higher pregnancy rates" it was recommended that at "peripheral centres it would be useful to prepack in sterilized disposal syringes".

Injectable contraceptives and Sexist bias- The Seventh Plan period was seen by the Govt. as a phase which was preparing for "conceptual

breakthrough. Apart from short and long term demographic goals like a crude birth rate of 27, crude death rate of 10 infant mortality of 67/1000 and a couple protection rate of 42% by 1990 and net reproduction of one by 2006 to 2011 and a zero growth rate by 2,050 they will strive to achieve other social goals like raise the marriage age, increasing literacy, employment of women, child survival and old age security. But what all this conceals is the govt's shift in emphasis. It began after the Emergency when women increasingly became the victim of the official FP programme. Reduction in vasectomies, increase in tubectomies, leading to the camp approach of laproscopic sterilization. Although the maternal and child health (MCH) component is a major plank of the FP programme, all available data on the health of women and children indicates that it continues to be poor. India reports lower life expectancy for women than for the men. It is also observed that the gender gap is widening with lesser share of gains received by women. Nor does "averting birth" improve quality of life for instance the nutritional level of children in Kerala which reports a high acceptance of family planning is far worse than that of children in U.P. In fact the FP programme has seen the woman not as major and human component of the family unit but only a breeder in society whose fertility must be controlled to achieve govt. targets even at a considerable risk to her health. Added to this has been the role of development agencies who since the 1970's have extended their welfare policies to include population control through family planning programmes. They have identified women in their reproductive role as essentially responsible for limiting the size of the family. They went to the extent of assuming that poverty can be reduced by simply limiting fertility achieved through widespread dissemination of

contraceptive knowledge and technology to women. Only the obvious failure of this approach led population planners (including Dr. S N Saxena and Coleman) to recognize that variables relating to women's status such as education and labour force participation could affect fertility differentials and consequently needed to be taken into consideration. (This change of approach partly took place at the behest of the World Bank which in its Development Report of 1984 states that by reducing infant & child mortality, educating parents (especially women) and raising rural incomes women's employment and legal and social status will prove a key incentive to fertility decline)

But even in this very "women centred approach" what strikes one is that women continue to be treated in an instrumental manner in population programmes. The recognition of links between women's autonomy over their lives and fertility control is not widespread or in the case of our country totally absent. The lack of satisfactory birth control methods and the introduction of more invasive techniques like injectables and implants is making birth control even more "women centred". As DAWN (1985) has argued this lets men off the hook in terms of their responsibility for birth control while increasingly placing the burden on women. A position which is also held by women's groups in India. And as stated by Dr. Raja Laxmi of AIIMS in the interview (which is a part of the material) that there is a fundamental lag even in the scientific and medical data on the male reproductive system. This coupled with the fact that controlling their cycle is more difficult and motivating them near impossible - has only made it easier to "let them off the hook".

But as we analyse the trial data, it will become evident that the women have developed their own version of ~~ambivalence~~ ambivalence towards the contraceptive technology. This is evident in the high discontinuation and drop out rates and unless the efficacy of any technology is proved in terms of positive health benefits and better adapted to the environment in which it is used it will ~~should~~ be opposed in every sense of the term. ~~absolute terms.~~

Anti Sterilization:

A recent editorial in Lancet has pointed out that "in third world countries like India where govts are so committed to the goal of population control there is often a neglect of basic ethical standards".

Given the conditions where surgeon vie with one another to complete larger and larger number of operations there is bound to be a failure to maintain standards of hygiene as well. As a result a large number of cases where patients have either lost their lives or have suffered damage due to lack of care at mass sterilization camps.

Between 1986-88 there were 344 sterilization deaths in the country. 447 - 1986-87 and 397 in 1987-88. Health Ministry reduces everything to statistics-death rate only 7.1 per one lakh sterilizations. In Orissa, Madhya Pradesh, Rajasthan and Gujarat the sterilization death toll is even higher. 13.5, 11.9, 11.8 and 11.2 per lakh sterilizations respectively.

All ICMR guidelines violated- laproscope not sterilized. No life saving drugs - no screening of patients with anaemia, hypertension and diabetes. Equipment not properly sterilized. In 1988 delegates from Karnataka, Maharashtra, Uttar Pradesh, Gujarat and Orissa who attended a meeting of Family Planning representatives from States which had more deaths than the national average (7.1) identified the main causes of death as septicemia, peritonitis, ~~meisitis~~ meningitis and tetanus.

An editorial in Lancet refers to a paper written by a surgeon who claims to have performed a total of 2,50,136 laparoscopic operations

~~in the usa~~

in the course of less than ten years in camps. A commentary on the same paper in the same journal indicates that the surgeon spent less than a minute on each operation. "The women were numbered by small stickers on their foreheads and then arranged in two long lines on the verandah of a school each leading to an operating bench. Even apart from the human angle, what of the post operational complications. Now there is enough epidemiological information to show that pelvic inflammatory diseases (PIVS) contribute significantly to gynaecological mortality. PIVS are a contra-indication for surgical intervention. Report of the Comptroller & Auditor General of India, 1983-84 for Maharashtra. In a test check the CAG has come across two ineligible cases of tubectomies on women whose spouses had already been sterilized.

The report found the state Govt. guilty of ignoring the G.OI guidelines specifying that laparascopic sterilization should be conducted only in well equipped hospitals and not in camps. In Maharashtra 94% of the laparoscopic tubectomies have been ~~xxxxx~~ conducted in camps. In several centres the operations has grossly violated State Govt. norms which lay down that not more than 50 operation should be conducted in one day with one surgeon and one laparascope. For sterilisations the State has recorded 90% achievement in 1983-84. Only half of the medical officers appointed for conducting sterilisation have received training. Similarly on 53% of the nurse midwives have been trained in the insertion of IUDs. Given these findings in a state with is reputed to have one of the better run health programmes it is not surprising that planners have started talking of a "target holiday".

Sterilisation Abuses in New Seema Puri resettlement Colony:

One classical abuse - 20 year old Putali who has no children was asked by the Doctors of the MCD dispensary in New Seemapuri resettlement colony that "If you want medicine for your headache you must get sterilized first".

A protest against such forms of coersion was organised by the Sabla Sangh. Putali and a few hundred women from this working class colony came together and demonstrated outside the dispensary.

The Sabla Sangh conducted a survey of four settlement colonies. Sunder Nagri, New Seemapuri, Dakshinpuri and Jahangirpuri to assess the state of health services in these areas. The data collected over a period of four years clearly showed that women were the worst affected and the direct victim of family planning methods and drives. General complaint was that there was no follow up care. Tubectomies Copper Ts and laproscopic methods were commonly used by Govt. hospitals. Chronic gynaecological ailments have developed in most women forcing them to depend on private medical help at great and usually unaffordable ~~expense to them~~ costs. Men are rarely sterilized. The medical authorities are using free medical health as a weapon for coersion.

New Seemapuri has a large refugee population from Bangladesh and Nepal. Kickshaw pulling, rag picking, construction work and the recycling of waste are the primary occupations of the residents.

Backache weakness, giddiness, abdominal pain, breathlessness and distension of the abdomen are the common ailments suffered by the women after the operation and 20% of the women surveyed had spent Rs.100-1000 on private medical care.

According to this study fifty per cent of the women sterilized failed to receive medical assistance after the operation resulting in medical complications.

In Rajasthan, Minister of State for Health admitted in the Assembly that 94 women had died following sterilisation operation since 1985. Of these 24 had succumbed to post operative complications.

International Family Planning Perspective - Vol. 15, No.3, Sept 1989:-

Assembly-line Sterilization:

One Indian physician has in the course of 10 years performed 250, 136 laparoscopic sterilisations. Reporting on his experience in the British Journal of Obstetrics and Gynaecology. Previn V. Mehta described having sterilized 40-50 women per hour in special sterilizatio camps with high levels of effectiveness (a failure rate of 0.1% and low levels of associated mortality 48 deaths per 100,000 procedures.) Furthermore rate of reported surgical and post operative complications were no greater than those in other large studies of female sterilizations. A British Family Planning expert John Gullebaud who observed Mehta's technique comments that "if the main criteria of success of a mass sterilisation program are safety, efficacy and cost effectiveness than Dr. Mehta and his team are to be congratulated. However he notes several reservations the greatest being the apparent paucity of counseling, lack of a human touch during the surgery and the risk of cross infection.

British Journal of Obstetrics and Gynaecology - 96: 1024, 1989
96: 1019, 1989.

People - 12 th May 1989 Norplant's US approval racommended.

The subcutaneous contraceptive implant, Norplant (Levonorgestrel) should be approved, the US, FDA's facility and maternal health drugs advisory committee unanimously recommended on 29th April.

The Population Council presented the results of the seven phase-III clinical trials involving 2,470 women between the ages of 18 and 40 from the US, Sweden, Finland, Denmark, Brazil, Chile, Jamaica and the Dominican Republican. Of this total over 300 were from the US. Two of the trials compared the product with an IUD. The Council also presented the findings from the use of the product in over 14,000 women who received it through "pre introductory" studies mainly in developing countries which were designed to give physicians experience with the system prior to approval.

Of the 2,470 women 400 completed the first five years of continuous use. Major reason for termination was irregular bleeding (17.4%) with menorrhagia. More than 12% of the women experienced 18 or more onsets of bleeding. Some women also reported amenorrhoea. 14.6% of women discontinued therapy for other complaints including placement related problems depression, mood changes, weight gains and headache. Problems with placement in 1.2% of women included infection and expulsion of one or more rods. Some women also complained that the rods were visible under the skin.

Potentially serious problems included hypertension (24 cases) ovarian cysts (14) cervical cancer (8) gall bladder problems (7) and aneamia (5) 6.7% of 992 removals resulted in complications. 101 accidental pregnancies occurred and the outcome of 27 pregnancies is unknown. One case of a birth defect was reported which consisted of ambiguous male genitalia.

A WOMAN-CENTERED APPROACH TO CONTRACEPTIVE RESEARCH AND DEVELOPMENT

Mahmoud F. Fathalla

A historical perspective

"When the woman is afflicted with a large wound as a consequence of an abortion, or the womb is damaged by strong suppositories, as many women are always doing, doctoring themselves , or when the foetus is aborted and the woman is not purged of the afterbirth, and the womb inflames, closes and is not purged, if she is treated promptly she will be cured but will remain sterile."

Hippocrates, 400 BC

Throughout human history, women have felt a need to regulate and control their fertility. Until the modern era, they neither had the power nor the safe and effective means to do so. The lack of tools did not prevent them, as the writings of Hippocrates (see Box) indicate, from trying to "doctor themselves", often risking their health, future fertility, and even their lives in the process.

In almost every culture historians have found ancient, traditional recipes which women have used. Egyptian papyri dating from 1850 B.C. refer to plugs of honey, gum acacia and crocodile

dung, used by women as a contraceptive vaginal paste (Speroff and Darney, 1992). Women traditionally had only one genuinely effective biologic method at their disposal to postpone pregnancy: prolonged breastfeeding. Whatever the effectiveness of these and other methods, their use by women throughout history demonstrates the serious intent with which women have pursued control of procreation.

Men, on the other hand, had the power and the means, very early in human history. The biblical story of O-nan is a case in point:

> *"And Judah said unto O-nan, Go in unto thy brother's wife, and marry her, and raise up seed to thy brother. And O-nan knew that the seed should not be his; and it came to pass, when he went in unto his brother's wife, that he spilled it on the ground, lest that he should give seed to his brother. And the thing which he did displeased the LORD: wherefore he slew him also".* (Genesis 38: 8,9,10).

The actions in the story are those of Judah, O-nan and the LORD. O-nan's brother's widow, Ta-mar, had no active role to play in this story. Withdrawal, or coitus interruptus, one of the most ancient methods, enabled men to exercise control over reproduction.

The condom, another effective contraceptive method, has also been available to men for a long time. The history of the

development of the condom is lost in antiquity but most versions indicate that it was a method developed by men for use by men. A popular version attributes its discovery to a "Dr. Condom", a physician in England in the 1600s (Speroff and Darney, 1992). The story goes that Dr. Condom invented the sheath in response to the annoyance displayed by Charles II at the number of his illegitimate children. Another version attributes the invention to a medieval slaughterhouse worker who conceived the idea that covering the penis with the thin membranes of an animal would protect promiscuous men from sexually-transmitted diseases (Himes, 1970).

In many societies, the predominant objection against contraceptive use was really to contraceptive control by women, rather than against contraception itself. Male-dominated societies resented giving control of the process of reproduction to women. Patriarchical societies reasoned that if women had control over their reproduction, they would also have the *unthinkable* - - control over their own sexuality.

Publications about the diaphragm first appeared in Germany in the 1880's. A practicing German gynecologist, Dr. C. Haase, wrote extensively about the diaphragm. Although Dr. Haase was prescribing the diaphragm for unhealthy women to protect them against undesired and risky pregnancies, he had to publish under a pseudonym of Wilhelm P.J. Mensinga (Speroff and Darney, 1992).

The diaphragm was named after the pseudonym.

The fact that women did not have control over their fertility affected their ability to enjoy mutually fulfilling sexual relationships. Marie Stopes noted that a popular demand of women at the time was for a simple pill or drug to make their husbands less rather than more passionate (Stopes, 1928). Women often said they liked everything about marriage, except "the going to the bed side of it" (Eyles, 1922).

Fertility by choice, not by chance, is a basic requirement for women's health, well-being and quality of life (Fathalla, 1993a). A woman who does not have the means or the power to regulate and control her fertility cannot be considered in a "state of complete physical, mental and social well-being", the definition of health in the constitution of the World Health Organization. She cannot have the joy of a pregnancy that is wanted, avoid the distress of a pregnancy that is unwanted, plan her life, pursue her education, undertake a productive career, or plan her births to take place at optimal times for childbearing, ensuring more safety for herself and better chances for her child's survival and healthy growth and development.

The Contraceptive Revolution

Widespread contraceptive use is a very recent phenomenon in

human history. The first demographic transition was accomplished in the Northern industrialized countries in the 18th and 19th centuries largely by men using coitus interruptus. Fertility in Europe and North America has declined gradually, and today has reached very low levels, in some places below replacement fertility.

The second demographic transition is taking place now largely in Southern developing countries. This transition began only in the past few decades and has depended substantially on a revolution in contraceptive technology. Among other things, women for the first time had methods which they could use, even independent of the cooperation of their male partners, to regulate their fertility and to enjoy sexual life without fear of unwanted ill-timed pregnancy. The consequent decline of fertility has been even more steep in the Southern than compared to the Northern countries. In the USA, it took 58 years for fertility to decline from 6.5 to 3.5; the same level of decline took 27 years in Indonesia, 15 years in Colombia, 8 years in Thailand and merely 7 years in China (UNFPA, 1991). Contraceptive users in the developing world increased ten-fold from an estimated 31 million couples in 1960-1965 to 381 million in 1985-1990 (UNFPA, 1991).

Before 1960, people had a very limited choice in contraception: between *coitally-related* methods (condom and

withdrawal for the male; diaphragm, cervical cap and vaginal spermicides for the female; ~~and~~ periodic abstinence for the couple) and *permanent* methods (female and male surgical contraception). The contraceptive revolution of the 1960s and 1970s led to significant improvements in existing methods, including the simplification of methods of female surgical contraception, to the extent that they no longer require general anaesthesia nor hospitalization. For the first time, ~~in human history~~, contraception could be taken out of the bedroom and out of the genital area, with the development of *systemic* hormonal methods.

In addition to the systemic oral hormonal contraceptives, which are short acting and administered daily, recent development of *long-acting* hormonal methods and the introduction of the intrauterine device (IUD) have freed women from taking a precaution at every sexual act, and provided an alternative to permanent contraception. Women now have methods that offer protection for 1-3 months (injectables), 5 years (Norplant®), or up to 8 years (IUDs).

A third major development is ***effectiveness***. While in the past, people had the choice only between coitally-related methods that are associated with relatively lower levels of use-effectiveness, and surgical contraception which is effective but permanent, women now have the choice of ~~modern~~ methods that are

highly effective and also reversible (pills, injectables, Norplant® and IUDs).

The fruits of the contraceptive technology revolution have ~~been enjoyed by~~ reached hundreds of millions of people all around the world: people living in the most varied circumstances, from the skyscrapers of Manhattan, to the peri-urban slums of Latin America, and the rural communities of the Indian subcontinent; people in all socio-economic strata; people with different cultures, religious beliefs and value systems; and people at different points in their reproductive lives (postponing a first pregnancy, spacing children or putting a limit on childbearing).

Whatever the underlying factors for fertility regulation, modern contraceptive technologies have given people the safer, more effective means to implement their decisions. Clinic and supply "modern" methods (defined as methods requiring supplies or clinical services and including male and female sterilization, IUDs, the pill, injectables, condoms and female barrier methods) account for approximately 80 percent of contraceptive practice worldwide (United Nations, 1988). The non-supply or "traditional" methods include rhythm or periodic abstinence, withdrawal (coitus interruptus), abstinence, douching and various folk methods. (It may be noted that the broad classification of clinic and supply methods as "modern" and of non-supply methods as "traditional" is not exact. The condom is an old method. Periodic abstinence

includes some new methods.)

The group of clinic and supply methods, which includes the highly effective methods that have revolutionized contraceptive practice over the past few decades and the methods most often offered by family plannning programs, make up a larger fraction of contraceptive use in developing than in developed countries - about 90 and 65 percent respectively. (See Table/Chart X - pie chart on worldwide contraception - page 7 of Fathalla, 1992b, in Reproductive health: A key to a brighter future, based on United Nations,1989). Indeed, the prevalence of traditional methods differs much more between developed and developing countries (24 and 6 percent respectively) than does the prevalence of clinic and supply methods, which is estimated to average 46 percent in more developed and 41 percent in less developed regions. This reflects the differing history of contraceptive practice in the two groups of countries. Whereas in most developed countries marital fertility reached low levels before modern contraceptives were invented, in most developing countries contraception was not widely practiced until modern methods were available, and these methods tended to be preferred by new users from the start (United Nations, 1988). In addition, these methods, particularly the clinic methods, were more widely promoted in family planning programs.

Box: "If all the people of the world are to enjoy the highest possible level of health and basic human rights, it is imperative that research on contraceptive development continues unhindered."

> Declaration of the International Symposium on "Contraceptive Research and Development for the year 2000 and beyond"

In the early days of the contraceptive technology revolution, the scientific community dreamed of an ideal contraceptive that would fit the needs of everyone, everywhere, every time. The field soon realized that a "magic bullet" is only a dream that cannot come true. The diverse needs of different people cannot be met by any single method but must be met by broadening contraceptive choice. A wide range of contraceptives is needed tailored to different human circumstances and desires: for people who are different, for circumstances that are different and for the same individual at different phases of life (Fathalla, 1990). Broadening contraceptive choice is thus a key to improving the quality of family planning services.

Contraceptives should not be looked upon as a temporary measure to ease the world population problem. Contraception will be a permanent feature of the way of life of all succeeding

generations on this planet. Our reproductive function is being voluntarily adapted to dramatic new realities. What we are witnessing is a major evolutionary jump that is science-mediated, rather than imposed by Nature.

The contraceptive technology revolution still has an unfinished agenda. The range of contraceptive choices needs to be broadened to meet the vast expanding and diverse needs for fertility regulation. Moreover, with all its benefits to the quality of life of women, the currently available contraceptive technology has left women with some genuine concerns as well as unmet needs. The qualities of convenience, effectiveness and use by women in modern contraception were not without trade-offs.

The modern contraceptive revolution has been largely demographic driven. Women have benefited in the process but were not in the center of the process. As far as policymakers are concerned, women were often means to an end, objects and not subjects. This has accentuated the suspicions of women's groups and resulted in a feminist critique of the medicalized contraceptive technology (Dixon-Mueller, 1993). Whether justified or unjustified, the critique must be voiced and must be heard, because the concerns are genuine.

Who is in control?

Women have more at stake in fertility control than anyone else. Contraceptives can be used by women to empower themselves by maximizing their choices, and controlling their fertility, their sexuality, their health and thus their lives. The convenience of long-acting and permanent methods is welcomed by many women. These methods, however, can be used and have been used by governments and others to control rather than to empower women. Some governments are short-sighted, not to see that when women are given a real choice, and the information and means to implement their choice, they will make the most rational decision for themselves, for their communities and ultimately for the world at large.

Safety concerns

Without safe abortion as a backup, the use of less effective contraceptive methods will not meet the needs of women in fertility regulation (Germain and Dixon-Mueller, 1992). As with any drug, increasing the effectiveness of contraceptives commonly has a trade-off in decreasing the margin of safety. From a public health point of view, contraceptive drugs and devices have an excellent record of safety. They have been used by hundreds of millions of women over extended periods of time and under varied circumstances. Few drugs have been, and continue to be, subjected to such scientific scrutiny as regards safety. This scrutiny is particularly important because, unlike those who use drugs to

cure illness, women (and men) who contracept are undertaking preventive action.

Safety concerns will loom particularly large if a service system is more concerned about demographic targets than about health and welfare of clients. Nonetheless, a contraceptive can be safe or unsafe, depending on who is using it and the quality of the service system delivering it. The technology "software" is as, or even more important than the "hardware" (Fathalla, 1991).

Moreover, the concept of safety should be demedicalized to reflect client concerns. A quality service should not define safety simply as survival. Nor should safety mean merely the absence of serious physical complications. Safety should be defined from a woman's perspective. So-called minor inconveniences or side effects such as menstrual bleeding disturbances, headache or weight gain may not threaten life, but can be of extreme concern and often significantly affect the functioning and quality of life of the woman (World Health organization, 1991).

The abortion dilemma

The contraceptive technology revolution has emphasized development of methods that are so effective that they can prevent the need for abortion. The rationale for this emphasis

derives more from political concerns than from health or scientific concerns. This focus on preventing abortion to the exclusion (until very recently) of work to develop post-ovulatory methods has serious implications for both health and fertility.

The abortion issue has implications for barrier method use that are particularly important given the STD/AIDS pandemic. Where safe pregnancy termination services are available and acceptable, the need for highly effective contraception becomes less, and women can more comfortably use barrier methods which will also protect against infection. Where abortion is illegal or unsafe, use of barrier methods can be associated with a high health risk to the woman.

A review of current abortion laws shows that some 52 countries, with about 25 percent of the world's population, fall into the most restrictive category, where abortions are prohibited on any grounds or allowed only when the woman's life would be endangered if the pregnancy were carried to term. 42 countries, comprising 12 percent of the world's population, have statutes authorizing abortion on broader medical grounds - e.g., to avert a threat to the woman's general health and sometimes for genetic or juridical indications such as incest or rape- but not for social indications alone or on request. Some 23 percent of the world's population lives in 13 countries which allow abortion for social or socio-medical indications. The least restrictive

category includes the 25 countries or about 40 percent of the world's population where abortion is permitted up to a certain point in gestation without requiring that specific indications be present (Henshaw, 1990). Even where abortion is legal, however, safe pregnancy termination services are not always available or affordable.

Unsafe abortion is one of the most neglected health and human rights problems in the world today. If there were a crisis in which 500 people died daily, in the world, there would be news coverage and perhaps a world uproar. Yet, no uproar has been made about the 500 women who lose their lives every day in pursuit of their reproductive freedom, because of unsafe abortion (Fathalla, 1992).

The current technology for pregnancy termination, even for *medical* pregnancy termination using mifepristone (RU-486), is still clinic-based. Its availability is limited by the availability of clinical services. It can also be an easy target for political opposition. Clinical facilities can be targetted for funding cuts, for p icketing or for worse. An effective, simple, affordable and safe technology which a woman can use in the privacy of her home, outside the health care system, is yet to be developed.

The unfair burden of fertility regulation

Women now have more reliable methods of birth control, but at a price. They have had to assume full responsibility for the inconveniences and risks involved. The role and responsibility of the male partner have receded when contraception was considered a woman's business. According to UN estimates, the percentage of different contraceptive methods among contraceptive users worldwide is as follows (United Nations, 1988):

Female:	
Female sterilization	26 percent
Intrauterine device	19
Pill	15
Vaginal barrier methods	2
Injectables	1
Other methods	2
Total	
Male:	
Male sterilization	10
Condom	10
Withdrawal	8
Male and Female:	
Rhythm	7
Total	

Women, therefore, assume responsibility for about two-thirds of contraception in comparison to men's 28 percent. For each male contraceptor, there are about three female contraceptors in the world. Not only do women have an undue burden of responsibility

in fertility regulation, but the methods which women have available for use that are associated with potential health hazards. The importance of male participation and responsibility has become much more with the emergence of the AIDS pandemic and the increasing prevalence of sexually-transmitted infections, where the use of the condom is the only effective strategy other than abstinence.

Reproductive tract infections: the silent tragedy

Fertility regulation is an essential component of reproductive health, but is not the only component. Women have other needs and other concerns that are often neglected. Of these needs, prevention and control of STDs is the one most linked with family planning. Both unwanted pregnancy and infection are transmitted through the same act of sexual intercourse, and women need effective protection against both.

One trade off to the wider use of modern, non-coitally related methods has been the decline in use of barrier methods that offer some protection against sexually-transmitted diseases (STDs). Reproductive tract infections, mostly resulting from STDs, are not only a major cause of morbidity in many women, but seriously undermine the quality of life of much larger numbers of women, particularly in developing countries (Germain et al., 1992). The worldwide spread of STDs has been one of the major

challenges to public health in the past few decades (Fathalla, 1992). While the burden of a number of traditional first generation venereal diseases like gonorrhoea, syphilis, and chancroid has declined, particularly in the industrialized countries, they have been amply replaced by new bacterial and viral syndromes associated with Chlamydia trachomatis, human herpes virus, human papilloma virus, and the human immunodeficiency virus (HIV). These agents, regarded as the second generation of sexually-transmitted organisms, are more difficult to identify, treat and control. Moreover, they can cause serious complications, which can result in chronic ill health, disability, or death. Both groups of STD's (the first and second generation) remain major health problems in most developing countries.

Reliable data on the worldwide incidence of STDs are not available. Minimal estimates by WHO of the annual number of new cases (not including HIV infection) are as follows:

Gonorrhoea	25	million
Genital chlamydial infections	50	
Infectious syphilis	3.5	
Chancroid	2	
Genital herpes	20	
Genital human papillomavirus infection	30	
Trichomoniasis	120	

STDs are now hyperendemic in many developing countries, including the rural areas where facilities for diagnosis and treatment are usually inadequate.

By definition, STDs affect both men and women. However, STDs have more serious sequelae in women than in men. Early detection and hence early treatment of STDs is easier in the male. In women, the lesions often occur in the inner genitalia and are thus hidden and quite often remain asymptomatic. Moreover, ascending infection in women has much more serious consequences, leading to pelvic inflammatory disease, higher risk of ectopic pregnancy, and permanent infertility. Cancer of the cervix is also a possible late sequela. Another consideration is the transmission to the foetus of several pathogens of STDs. It is also not widely appreciated that the risk of transmission of STDs is much greater from man to woman than the other way round. Finally, the most effective method available for protection against STDs, the condom, is controlled by men. An effective method of protection, that a woman can use without the need or necessity of her partner's cooperation, simply does not exist. The female condom, under development, requires male cooperation and is also likely to remain prohibitively expensive.

To meet the closely interrelated needs for birth control and disease prevention, a second contraceptive technology revolution must occur, driven by women's needs and women's perspectives. A woman-centered approach to contraceptive research and development requires a clear *mission*, a reinvigorated *science*, and sustained *resources* (Fathalla, 1993b).

The mission

The first contraceptive technology revolution was demographically driven, with emphasis on the development of methods that can have a demographic impact by being effective, long-acting and widely available. The field of contraceptive research and development is best described now as opportunity-driven, rather than goal-driven. Because of poor funding, scientists follow whatever leads present themselves, and industry seeks only to make marginal improvements or modifications in already existing products. For the second contraceptive technology revolution, the field must again be goal-driven, and the goal should be set right. The field should sharply focus on a sustained effort to develop contraceptives that address the still unmet needs of women. The demographic impact will not be lost; it will be enhanced. The message for all of us concerned about

population growth should be clear: Women Mothers know best. It is their bodies, their lives and their children's lives that are at stake (Taylor, 1993). Respecting women and responding to their unmet needs is one of the best strategies for saving the planet.

A recent survey of the field of contraceptive research and development has come up with a list of 94 product leads that are currently being pursued (PATH, 1993). Many of these are variants of existing methods or alternatives within existing contraceptive approaches. They include, among others, 4 IUDs, 7 hormonal implants, 5 hormonal injectables, 5 oral hormonal contraceptives, 6 vaccines, and 6 techniques for female sterilization.

Given financial constraints among other reasons, a strong case can be made for the field to focus its efforts on these urgent needs that are met poorly, if at all by existing technologies (protection against infection, postcoital/ post-ovulatory methods, male methods). The field must have the courage to drop leads, even if they are scientifically feasible, and to break new scientific ground. Scientific opportunity should not be the sole driving factor; rather scientific work should be pursued within priority areas of need.

Creating common ground

Collaboration between the users of the technology and the

creators of it is essential. This requires development of communications and trust through honest and straightforward dialogue. For example, the WHO Special Program of Research, Development and Research Training in Human Reproduction and the International Women's Health Coalition initiated such a dialogue in 1991, by convening a meeting of women's health advocacy groups from developed and developing countries and scientists engaged in contraceptive research and development. The meeting proved not only that scientists and women's health advocates can listen to each other and respect each others' views even when they differ, but also that a common ground can be created for future collaboration (World Health Organization, 1991).

It is time that this dialogue is moved forward and that mechanisms are institutionalized to ensure that the voices of women are not only heard but also heeded. Women's health advocates and potential users should be represented in all decision-making mechanisms and advisory bodies that are established to guide the research process - including definition of criteria for safety, determination of research priorities, design and implementation of research protocols, setting and monitoring of ethical standards, and decisions on whether to pursue a fertility regulation method from one stage to the next, especially decisions to move from clinical to introductory trial to introduction of a method into family planning programs (World Health Organization, 1993).

Priority needs

An international symposium on "Contraceptive research and development for the year 2000 and beyond" was convened in Mexico City in March 1993. The symposium brought together senior managers of all the international and some national public sector agencies that undertake contraceptive research, along with program directors and senior staff of international and national agencies that support or are otherwise involved in the field of fertility regulation research, together with women's health advocates. A clear recommendation was that *"Particular emphasis and priority should be given to methods that coincide with the women's perceived needs and priorities, including among others, methods that are under the user's control and that also protect against STD's, post-ovulatory methods, and safe male methods that enable men to share responsibility for fertility regulation and disease prevention."* (World Health Organization, 1993)

The need for methods which women can use to protect themselves against STDs, including HIV, has become urgent. Available female barrier methods are not very effective as contraceptives, and are even less effective for protection against STDs. Moreover, their use still depends on cooperation of the male partner. There is also no method which can protect women from infection while still allowing them to become pregnant. It is quite common, for women to get the infection from their

husbands who have multiple sexual partners. The need is for effective methods which women can use and control without the necessity for partner cooperation. It is possible that if such methods become available, women will do better than men in compliance, providing more hope for the control of the pandemic of STDs.

Carl Djerassi, a father of the oral contraceptive pill, has recently remarked that if he were to choose one single new contraceptive to develop, it would be a once-a-month pill effective as a *menses-inducer* (Djerassi, 1991). Instead of currently used oral contraceptives, which are taken daily for most of the month, a menses-inducer would be taken by a woman only during those months when she had unprotected coitus. Instead of waiting to see whether she had missed her period, a woman would take a single pill (containing a short-lived and rapidly metabolized drug) to induce menstrual flow at the expected time. Although not acceptable or suitable for every woman, such a regimen would be an enormous improvement for many (Rimmer et al., 1992). At most, a woman would take 12 pills annually, rather than the present 250 or more. With such a pill, women would not know whether they carried a fertilized ovum. A most important feature of such a method is that the decision to contracept is made post-coitally. For some women, the menses-inducer would be an attractive back-up to barrier contraceptive methods, thus encouraging their wider use. A menses-inducer would also be

suited to the particular needs of adolescents. A menses inducer, that is completely user-controlled, could also provide a technological response to the abortion controversy. It could transfer the issue from the public domain to the privacy of the individual's moral code. To have a real impact, a menses-inducer must be safe enough to be used at home outside the health care system.

Women ~~for biological reasons~~ have to carry all the burden and risks of pregnancy and childbirth. This, however, is no reason that they should also carry most of the burden of fertility regulation. A sustained research effort is needed if *men* are to have broader contraceptive choices to enable them to share effectively in the responsibility for fertility regulation. For biologic reasons, regulation and control of the male reproductive process is more difficult than in the female. Hormonal suppression of spermatogenesis may be feasible, but unless associated with replacement hormone therapy, sexual potency will also be suppressed. A better understanding of mechanisms involved in the post-testicular maturation of sperm, without interference with spermatogenesis and testicular hormonal production, utilizing the new tools of molecular and cell biology and biotechnology, can provide promising leads for the systemic male contraceptive of the future. The ease with which clinical studies on methods of male fertility regulation attract volunteers is an indication that the new generation of men is

more ready take on its responsibilities than has been generally believed (Waites, 1993).

Reorienting
Reinvigorating the science

This Contraceptive 21 Agenda requires that advances in cell and molecular biology and biotechnology be applied to fertility regulation. While such advances have opened new frontiers in the medical and biological sciences, contraceptive research and development have yet to exploit them. Major and sustained investment in human resources is required to build up a critical mass of scientists active in the field. Investment in the field of reproductive endocrinology provided most of the leads for the first contraceptive technology revolution. The field is now ripe for another major initiative.

Resources

Although estimates of global expenditures for contraceptive research and development are difficult to obtain, it is clear, contrary to what some people believe, that contraceptive research and development are poorly funded. The most complete study of the levels and sources of worldwide funding for contraceptive research and development reports on trends only up to 1983 (Atkinson et al., 1985). That study estimated that $63 million was spent for contraceptive research in 1983. This figure

included funding for the evaluation of long-term safety of existing methods. Of this total, private industry spent an estimated $22 million or about 35 percent, and specialized public sector agencies spent, out of funds given by international donors, an estimated $26 million or 41 percent of worldwide expenditure. The remaining 24 percent of expenditures was provided mainly by national governments that funded mission-oriented research. Less developed countries, **especially China, India, Chile and Mexico** contributed about one percent of the total. There is no evidence that the overall picture has changed very much since then. An assessment in 1993 **estimated** the worldwide **annual** funding for contraceptive research and development at about $57 million (PATH, 1993).

Global expenditure on contraceptive research and development, from all sources, is less than 3 percent of global contraceptive sales, estimated to be between $2.6 billion and $2.9 billion (PATH, 1993). The funding of public sector programs of contraceptive research and development represents about 3 to 4 percent of the international assistance for population and family planning, estimated in 1990 to be $802 million (UNFPA, 1992). Another figure to note in these budgetary considerations is that about $230 million is estimated to be required to bring a new chemical entity **for human use** from research to the market. (See figure of steps of the process of contraceptive research and development)

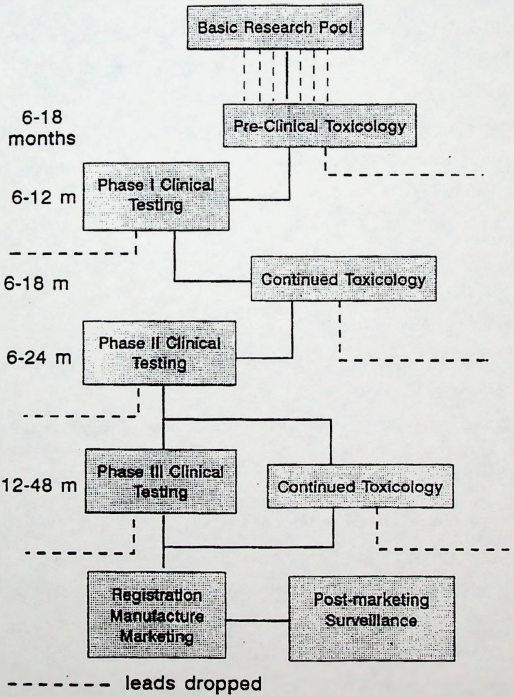
Public resources available for family planning and reproductive health are limited and badly needed to expand access and improve the quality of fertility regulation services. Thus, any major infusion of resources in the contraceptive research and development field will have to come from private industry, which has finance and expertise far greater than other sources. The pharmaceutical industry in the developed world invests about 16 to 19 percent of revenues in research and development of new products (Pharmaceutical Business News, 1992). U.S. and European companies report total revenues of over $90 billion per year and a projected annual growth of 9 to 10 percent over the next five years, implying that significant resources could be made available for research activities. The constraints that earlier led to the retrenchment of industry from the contraceptive field must be addressed, however, to mobilize their vast resources (PATH, 1993). Foremost among these is a perception of the market as being "mature" i.e. saturated in developed countries and not profitable in developing countries, as well as a perceived dearth of dramatically new product ideas. Product liability, drug regulatory requirements and a hostile political climate played a secondary role as disincentives to industry. The market is changing. High rates of unwanted pregnancy, as well as a heavy reliance on sterilization among the younger population, suggest a "latent demand" for new contraceptives. Public sector provision of contraceptives in many developing countries is now giving way to a mor significant role for the private sector, and as market

economies in developing countries evolve, there will be a progressive increase in the share of the private commercial sector, brightening future profit prospects. Drug regulatory requirements are now more streamlined and rationalized. The political climate, particularly in the US, seems to be easing. Public sector contraceptive research and development programs are needed for re-engaging industry on a larger scale, by focussing on long-term strategies to develop new product ideas that respond to currently unmet needs of women, and that whet the appetite of private industry. Public and private sector collaboration needs to be promoted.

Conclusion

Will women get the contraceptives they still need to pursue their reproductive rights and reproductive health?. The answer is yes, when the contraceptive research and development field becomes mission-oriented, when women participate actively in the process, when science is re-invigorated, and when the required resources are mobilized particularly industry resources. Women in the 21st century deserve a better deal. Political will can make it happen, and the time to start is now.

Fig. 3
Steps in Contraceptive Research and Development



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