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RESEARCH IN THE FIELD OF REPRODUCTIVE BIOLOGY AND CONTRACEPTIVE TECHNOLOGY

Indian Council of Medical Research has been supporting research in the field of reproductive biology and contraceptive technology for a number of years. Work on these aspects was undertaken mainly at the Council's Institute for Research in Reproduction (IRR), Bombay, and also at many other institutions all over the country. Research activities in this field can be broadly classified as contraceptive research, application oriented basic research and developmental research.

CONTRACEPTIVE RESEARCH

INTRAUTERINE DEVICES

Ample evidence exists today to indicate that no single intrauterine contraceptive device (IUD) made from an inert material has advantages over others. Pregnancies, expulsions, removals have been variable with different devices. Studies have shown that larger the surface area of the device, the lesser the number of pregnancies, but greater the number of removals because of bleeding and pain. Unlike the rate of metrorrhagia, expulsion rate has been suggested to be inversely proportional to the rigidity of the IUD. The 'T' device was originally introduced with a view of providing a design which could best adapt itself to the uterine cavity even when it contracted maximally. Results of preliminary investigations showed that the 'T' device made of polyethylene produced 5 times less pain and bleeding and had about half the expulsion rate when compared with the Lippes loop. However, pregnancy rate was higher.

Because of the lower incidence of the side effects with the 'T' device and the finding that intrauterine copper had antifertility properties, the idea of utilization of the 'T' device as a carrier for copper emerged and the 'second' generation of IUDs developed. Evaluation of the efficacy and safety of several of these devices was, therefore, undertaken with a view to be able to provide an IUD which would be better accepted than the Lippes loop.

Copper T 200:

Clinical trials with Copper T (CuT) 200 were initiated at 19 centres. A total of 4,357 women were observed for 82,384 woman months. Majority of acceptors were in the age group of 20-34 years, and had borne 2-3 children, indicating that the intrauterine device was by and large used as a method for spacing. It was also seen that fewer women who had no living son came for insertion as compared to those who had no living daughter. The number of acceptors who had no living son was lower irrespective of the number of living daughters, supporting the hypothesis that most couples desired atleast one male living child.

The net cumulative rate for pregnancy at the end of 54 months was 1.8 per 100 users which did not increase substantially after the first year of use. Expulsion and bleeding episodes were more frequent in the first year and declined during successive years of use. Expulsions were more frequent in the grand multiparous women. Pelvic infections were observed mainly during the first two years of

use. There were four perforations. Continuation rate at the end of 54 months was only 25.5 per 100 users. Removals due to non-medical reasons such as planning pregnancy, husband/family objections, lack of confidence and change to other methods were 42.0 per 100 users.

Copper coils were found broken and fragments missing in many devices that were removed after 4 years. This device is presently being used in the national programme. Changing of the device after four years has been recommended.

Copper T 220:

In order to lengthen the life span of the device and to reduce expulsions by making the device more rigid, copper wire was replaced by copper sleeves (CuT 220). Clinical trials with CuT 220 were initiated and a total of 875 women were observed for 10,724 woman months. Analysis of data at the end of 24 months, using life-table method, gave a net cumulative continuation rate of 55.7 per 100 users. Pregnancy was 0.2, and expulsion-displacement 8.9 per 100 users. Performance of this device was in no way superior to the CuT 200. Replacement of the latter device after 4 years ensured to some extent, contact with acceptors who would otherwise have been lost to follow-up.

Copper T 380 and Copper Y devices:

Randomized trials with CuT 200, CuT 220, CuT 380 (combination of copper wire and copper sleeves) and CuY were also initiated. These were evaluated in the (i) post-abortion (concurrent) and (ii) non-puerperal groups. Analysis of data at 12 months indicated that the cumulative rate for expulsion-displacement and bleeding was higher with all the devices in the post-abortion group as compared to non-puerperal group.

In the post-abortion group expulsions were least with CuT 200 (8.2 per 100 users) and maximum with CuY (17.3 per 100 users). The difference was statistically significant ($P < 0.05$). Expulsions with CuT 220 and CuT 380 did not show significant difference when compared with CuT 200. Although bleeding was higher with CuT 220 as compared to CuT 200 and CuY, this difference was not statistically significant. No pregnancies occurred with CuT 200 and CuY. In the non-puerperal group, expulsions were least with CuT 200 and maximum with CuY ($P < 0.05$). CuT 380 also gave higher

expulsions as compared to CuT 200 ($P < 0.05$). Bleeding was less with CuT 200 and CuY and maximum with CuT 220. A total of 4 perforations occurred, one each with CuT 220 in the post-abortion group and CuY in the non-puerperal group, and the remaining 2 occurred with CuT 200 in the non-puerperal group.

Comparing the overall performance of these devices in both the groups, CuT 200 appeared to be a better device with regard to expulsions and side-effects. Although bleeding was less with CuY, higher incidence of expulsions and breaking of the terminal thread made it less suitable for practical use. Addition of more copper in the CuT 220 and 380 did increase the efficacy of the device but side-effects such as bleeding and pain were observed more frequently. Furthermore, the rigidity of the device did not lower the incidence of expulsion to a meaningful extent.

Copper T 200 Ag:

Long-term study with CuT 200 has indicated that the copper wire tends to fragment when it is left *in utero* for a period of more than 4 years. To avoid this complication, a new copper T device, where the core of the copper wire is made of silver, was investigated. This pilot study compared the new device with the standard CuT 200 with regard to safety and efficacy. A total of 199 women were enrolled. CuT 200 was inserted in 101, CuT 200 Ag in 98. Data analysis at the end of six months indicated that expulsion and bleeding were slightly higher with CuT 200 Ag, as compared to CuT 200.

Long term effects of IUD:

At the request of the Department of Family Welfare, Ministry of Health, a collaborative study was undertaken to investigate the effects of intrauterine device used beyond five years. Data were collected from 10 centres on 1,181 women. Complaints such as cramps, backache, bleeding and vaginal discharge varied between 12 to 26 per cent during the first year and gradually declined with time indicating that the 8 years use of the device did not have a serious deleterious effect.

HORMONAL CONTRACEPTIVES

The combination oral contraceptive pill is still the most effective large scale method

available for fertility control. While oral pills are still popular in western countries, the wide acceptance of this method in our country is still debatable. There is, therefore, a constant search for developing a method which would obviate the need for motivation for daily pill intake.

Injectables:

Although use of a large dose of norethisterone enanthate intramuscular injection once every three months has been favoured by women in many countries, side-effects such as irregular bleeding, has dissuaded its use. Therefore, phase II trials using one-tenth the amount as monthly injections, were initiated with the objective of achieving antifertility effect without inhibiting ovulation - an approach similar to the mini pill. Preliminary six month data analysed by life-table method, on extended trial with norethisterone enanthate 20 mg monthly, on 213 women observed for 728 woman months gave a net cumulative rate for pregnancy of 5.0 and closures due to menstrual disorders 19.4. Bioavailability and endometrial histology studies are in progress.

Biodegradable pellets:

One of the major disadvantages of using oily preparations is the need for the relatively frequent administration of the drug. The use of subdermal implants made up of silastic capsules containing steroids was considered as an alternate approach. However, migration from injection site and difficulty in removing the empty capsule are its major drawbacks. To overcome these, biodegradable polymers incorporating steroids have been suggested as a method for the slow release of the drug from the injection site. The Council is at present evaluating the efficacy of pellets which contain 85 per cent steroid in combination with cholesterol.

Vaginal rings:

A new approach for delivering the progestogen at low dose levels is the vaginal ring. These rings are made of silicone polymer containing the steroid, which is slowly released and absorbed through the vaginal mucosa.

The efficacy and safety of two types of rings are being tested - one containing norgestrel alone; and the other norgestrel in combination with estradiol. Release of steroids from both types of rings inhibit ovu-

lation. So far, results have been satisfactory with vaginal rings containing estradiol. Pharmacokinetic and bioavailability studies with these rings are in progress.

Studies on bioavailability:

Despite the widespread use of oral pills, little is known regarding the bioavailability of steroids under different nutritional conditions. This information is considered very important for assessing the correct dosage of contraceptive drugs so that toxic side-effects could be minimized in malnourished populations.

Bioavailability of steroids from vaginal rings containing norgestrel was done at the National Institute of Nutrition, Hyderabad and Institute for Research in Reproduction, Bombay. Blood levels of norgestrel (dNg), progesterone and estradiol were estimated. dNg levels ranged from 1 ng to 3 ng/ml in all subjects. Cervical mucus score remained low in all the cycles. Plasma levels of progesterone and estradiol were found to be very low indicating suppression of steroidogenesis and ovulation.

Bioavailability of steroids from biodegradable pellets was estimated at the Institute for Research in Reproduction, Bombay. After an initial spurt, release of steroids was found to be steady during the 6 month period of observation. These studies are in progress.

Studies to determine the bioavailability of steroids with norethisterone enanthate (NET) 200 mg given 3 monthly were carried out at Chandigarh and Calcutta. Results have indicated that peak norethisterone levels are attained by 2nd week reaching low levels by 8th to 12th week. Endometrial biopsies showed atrophy of endometrium in some women which was accompanied by low levels of plasma progesterone.

Bioavailability studies were also carried out with low dose oral pills (NET 0.35 mg and 1.0 mg). Results indicated that the steady state levels reached with both were almost in the same range after 12 hours. At the National Institute of Nutrition, Hyderabad, data on women who received a single pill containing 0.35 mg NET indicated that the rate of drug elimination was related to wt/ht^2 and skin fold thickness. However, these observations have to be confirmed on a larger number of women before any such relationship can be considered established.

It is proposed to extend all these studies to malnourished women.

Effects of hormonal contraceptives on the immunological status of women:

Studies on experimental models as well as the human host have demonstrated that hormonal agents alter the immunological response - humoral as also cell mediated - to bacterial antigens. These responses would be governed by the genetic make up of the host, the nature of the antigen against which the immunological response is directed, and also the biological activity and the chemical nature of the hormone. Earlier work had indicated that combination type of hormonal steroids when administered for long periods lowered the immunological response even to a potent immunogen as tetanus toxoid. Current investigations have indicated that neither HI nor CMI to typhoid vaccine was altered in women who used hormonal contraceptives for a period of only 3 to 4 months. The immunological consequences of long term use of hormonal contraceptives are presently being investigated. This information would prove invaluable and would indicate the need or otherwise of additional prophylactic care of women using hormonal contraceptives.

Interaction of steroids with other health variables:

A study on the interaction of contraceptive agents and methods with nutritional, infectious and other health variables was carried out at two ICMR centres. The main aim was to find how women with lower nutritional status reacted metabolically to steroidal contraceptives. So far, 430 subjects are being followed up at regular intervals. Basal levels of the parameters studied before starting the therapy have been established. Uptill now, data on 91 patients have been obtained with respect to all parameters. Preliminary results indicate that worm infestations did not adversely affect plasma steroid levels. Attempts to assess the effect of oral pills on vitamin B status indicated that these potent antifertility agents might create a sub-clinical vitamin deficiency state in the host. The effect of oral pills on the levels of other vitamins is under investigation.

Centchroman:

Clinical trial with Centchroman developed by CDRI, Lucknow as an antifertility agent was undertaken. A total of 205 women were given

120 mg centchroman weekly and were observed for 674 cycles. The trial was discontinued as 25 women became pregnant. Most of these pregnancies occurred during the first cycle of use. Therefore, phase II trial was initiated with 60 mg weekly schedule with an additional tablet administered on the first day of the menstrual period. Similarly an additional tablet was given on the first day of all subsequent cycles. No pregnancies have occurred in the 59 women observed so far. Irregular cycle control appears to be the major problem. Pharmacokinetic studies with 45 mg are in progress.

Technical evaluation of IUD/oral pill national programme:

Technical evaluation of the IUD/oral pill programme was initiated at the request of the Ministry of Health & Family Welfare, with the objective of evaluating the practical usefulness of different contraceptive methods in the existing infrastructure of the National Family Welfare Programme. This would thus enable necessary midcourse corrections for the proper implementation and better acceptance of these programmes in the country. Several centres in the country were selected. Equal number of rural and urban clinics, under the administrative control of State Family Welfare Bureaux were attached as feeding units to each of the coordinating centres. Enrollment was much below the anticipated number and only 2,659 women got IUD insertions done and 833 registered for oral pills. Analysis of data at six months gave a lower net rate for expulsion and bleeding as compared to the results of the larger study conducted by the ICMR contraceptive testing unit network. Removals due to personal reasons were maximum, although the overall continuation rate was better. The validity of these conclusions warrants a larger number of acceptors with long follow-up. Of the 833 pill users, continuation rate at the end of six months was 74.5 per 100 users, discontinuation due to medical reasons 13.4 per cent and personal reasons 11.3 per cent.

CONVENTIONAL CONTRACEPTIVES

The modern contraceptives either hormonal preparations or intrauterine devices are contra-indicated in some women because of their endocrine status or due to other reasons. Therefore, the improvement in the efficacy of conventional contraceptives cannot be ignored. The IRR, Bombay, therefore, continues to do the laboratory and clinical

testing of jellies, creams, foam tablets and other drugs.

LONG TERM EFFECTS OF STERILIZATION PROCEDURES

The evaluation of the long term effects of sterilization methods is extremely important with reference to the health and well-being of individuals accepting these procedures.

Tubal sterilization:

Morbidity following tubal sterilization depends upon several factors, timing of sterilization and other surgical procedures done concurrently. In India, medical facilities vary considerably from region to region and from hospital to hospital. It was, therefore, considered necessary to evaluate the minimum facilities and expertise required for performing tubal ligations with least complications. With this in view, a multicentric study was initiated to collect data on the incidence of non-fatal early and late complications following tubal sterilization, on a countrywide basis.

A total of 21,772 cases have been enrolled so far, and preliminary screening of these cases showed that 37.5 per cent of the sterilizations were done in the post-partum period, 28.8 per cent were concurrent, of which 24.3 per cent were concurrent with abortion and 4.3 per cent concurrent with caesarean section. 29.5 per cent sterilizations were done in the interval period, 4.0 per cent in post-abortal period and 0.2 per cent in the antenatal period. In most of the cases (76.6 per cent) the procedure for sterilization was laparotomy, followed by laproscopy in 16.7 per cent of cases. Techniques used for tubal ligation were Pomeroy in 78.1 per cent of cases and electrocoagulation/electrocauterization in 15.8 per cent. In the remaining cases, techniques used were salpingectomy, Uchida, rings, clips, etc. or a combination of two techniques. The study is presently in progress and detailed analysis on the short and long term sequelae will be available only after completing the enrollment of all the 30,000 cases.

Vasectomy:

A cross-sectional study was carried out on the hormonal, physiological, and endocrine status following vasectomy. Gonadotropin, testosterone and oestrogen levels were assayed using radioimmunoassay techniques. Results

revealed that there were no significant changes in the circulating levels of either gonadotropins or oestrogens. The androgen levels in some cases however, showed a slight increase. These results indicate that vasectomy does not adversely affect the hormonal status. The study on the other hand revealed that vasectomy might lower prostate function, as evaluated by the activity of the enzyme maltase, which is present in semen. The results further suggested that vasectomy might prevent benign hypertrophy of the prostate. A study in a larger group needs to be carried out to confirm these preliminary findings.

Immunological status following vasectomy:

Research on the immunological consequences of vasectomy has revealed that humoral (circulating antibodies) as well as cell mediated immunity (CMI) to spermatozoa develop in some individuals following vasectomy. It was, however, noted that the immunity was not directed against any other organ or cell of the body. Such immunity to spermatozoal antigens has also been encountered in certain cases of male infertility.

ANTIFERTILITY DRUGS AND PLANTS

Drugs:

The antiandrogen cyproterone acetate, has been shown to inhibit fertility in the male rat as also man. Results of the studies at the Institute for Research in Reproduction, Bombay, with cyproterone acetate and another antiandrogen flutamide, have indicated that the latter would be the better choice for inhibiting male fertility because the compound does not have any hormonal activity in comparison to cyproterone acetate, which has some progestational activity.

Studies with α -chlorhydrin, cyproterone, and danazol were undertaken at the University of Rajasthan, Jaipur, to study their antifertility effect. Studies on α -chlorhydrin led to reversible male sterilization with normal liver function. Synergistic action of two different drugs α -chlorhydrin and K1-33828 (Methallibure) was also studied and found to be effective in inhibiting spermatogenesis. Antifertility effect of α -chlorhydrin was also studied on human ejaculated spermatozoa. It was found that α -chlorhydrin caused inhibition of sperm motility *in vitro*, as shown by a significant drop in motility of sperms at a concentration of 30 mg and 40 mg per cent.

Plants:

Of the various plants screened, three, namely *Embelia ribes*, *Piper longum* and *Lawsonia inermis* significantly inhibited pregnancy in female rats. Antifertility activity of the various extracts of *E.ribes* have however not given conclusive results. The aqueous and alcoholic extracts obtained after cold percolation have failed to show any contraceptive effect. Studies in monkeys have indicated that larger doses of *E.ribes* are necessary to inhibit spermatogenesis than for the functional depression of the accessory sex glands.

Screening of plants for antifertility drugs has also been carried out at the Central Drug Research Institute, Lucknow and College of Veterinary Sciences, Tirupati. It was found that seeds of *Crotalaria juncea* Linn possess 83.3 per cent antifertility activity in albino rats. This is being further investigated. Two other plants which have been investigated are *Pittosporum nilghrense* and *Caltha pulu-stris*. On systematic fractionization of these plant extracts, four saponins were obtained which showed spermicidal action against rat and human spermatozoa.

With a view to finding an oral non-toxic indigenous drug with antifertility effect, two fractions from the extract of the roots of the plant *Aristolochia indica* were investigated at the Indian Institute of Experimental Medicine, Calcutta. The extracts studied were sesquiterpene and methyl ester, both were found to have abortifacient effect in early pregnancy. Sesquiterpene also had an anti-implantation effect at a certain dose level. The compounds were subjected to toxicity studies and found to have very little toxic effect.

Indigenous preparations:

During the year, several indigenous preparations were evaluated. These included *Garbh Ripu*, *Karkoti*, *Banjhour*, *Neerodhak Vati*, *Biswajit*, etc. Of those tested, none has so far proved to be as effective as claimed.

STUDIES ON ABORTION

Study on sequelae of abortions:

The demand for abortion - for medical, eugenic, humanitarian and social reasons - has progressively increased since the enactment of the Pregnancy Termination Act in 1972. Any

procedure used to induce an abortion may impair health if it is not selected and carried out properly. Therefore, abortion is emerging as a potentially important maternal health issue. The incidence and severity of complications associated with abortion are related to several factors, e.g. period of gestation, method used, operative facilities, operator's experience, etc. Although several investigators in India, have reported their data on complications following abortions, it was difficult to compare or compile these results because of the great disparity in the methodology for data collection and reporting. Incidence of rare complications of commonly used methods and complications of comparatively infrequently used methods could not be assessed from these small studies. Realizing the need for obtaining data on the safety of various procedures in a comparatively short time, a multicentric nationwide prospective study was undertaken in 16 teaching hospitals on the sequelae of abortions.

A total of 17,628 women who had medical termination of pregnancy (MTP) were enrolled for the study. Majority of abortion seekers had pre-college or college education and came from families with per capita income Rs.30-150 per month. Seventy per cent were between 20-35 years of age. Teenagers requesting abortion formed only 5.2 per cent and unmarried nullipara constituted less than 8 per cent. Over 90 per cent of women were married and had one or more children and 37.5 per cent had 3 or more children at the time of MTP. Women who gave history of previous induced abortion formed only 6.5 per cent.

Majority of the women came for MTP during first trimester (85.9 per cent). Second trimester abortion seekers consisted mainly of illiterate women from lower socio-economic group, single or widowed women, teenage nullipara, and grand multipara beyond 35 years of age. Suction evacuation was the most common method used for inducing abortions (71.1 per cent), followed by D&C (11.7 per cent), hysterotomy (6.0 per cent), intra-amniotic saline (2.9 per cent), prostaglandin instillation by various routes (7.1 per cent) and extra-amniotic rivanol (0.9 per cent). Prior to abortion, only 24.2 per cent of the abortion seekers had used some form of contraception. However, 63.1 per cent accepted effective concurrent contraceptive measures at the time of abortion.

Overall incidence of immediate complications at the time of MTP were low. Haemo-

rrhage (3.3/1000), cervical injury (1.3/1000), uterine injury (3.1/1000), other organ injury (0.7/1000). Other major complications were noted in 2.2/1000 and minor complications occurred in 31.3/1000. Infection was the most commonly noted delayed complication. Pelvic infection occurred in 26.6/1000, urinary infection in 3.5/1000 and other infections in 19.9/1000. Incidence of incomplete abortion at follow-up was noted in 14.0/1000. Other major complications were reported in 1.7/1000 cases. Post-abortion bleeding in 13.9/1000 and minor complications like abdominal pain, vaginal discharge *etc.*, occurred in 105.4/1000 cases.

Analysis of complications in relation to methods used in the first trimester abortions, showed that D&C and suction evacuation were the two common methods used for the induction of abortion during the first trimester. In the overall analysis, D&C and vacuum suction appeared to have similar complication rates but severity of complications seemed to be greater in the D&C group. Methods used for second trimester abortions included intra-amniotic saline, prostaglandin instillation by various routes and hysterotomy.

Termination of pregnancy during first trimester was found to be safer than termination during second trimester. Even within each trimester, there was a progressive increase in the incidence of both immediate and delayed complications with increasing period of gestation. Termination done earlier than 8 weeks of gestation had the lowest incidence of complications while termination of pregnancy beyond 16 weeks had the highest complication rate.

Analysis of complications in relation to concurrent contraception indicated that tubectomy done concurrently with abortion appeared to be associated with an increase in some of the immediate complications like injury to other organs and anaesthetic complications. Among the delayed complications, infections were more common in the concurrent sterilization group inspite of prophylactic antibiotic therapy. Concurrent IUD insertion was not associated with any increase in sepsis rate. However, incidence of post-abortion bleeding was higher in the concurrent IUD acceptor group. Concurrent pill acceptors and non-acceptors of contraception had the least rate for delayed complications.

Among women who did not accept contraception at the time of follow-up only 20.5 per

cent accepted some form of effective contraception at 3 months. It is conceivable, therefore, that among those who did not accept contraception at the time of abortion, the risk of unwanted pregnancy and subsequent requests for repeated abortions would be substantially higher.

Prostaglandins:

Although effective methods are available for the termination of first trimester pregnancy, a large percentage of women seek second trimester abortions. The available alternatives for this group include hysterotomy, hypertonic saline, urea and prostaglandins. Hysterotomy is a major surgical procedure which has its own associated risks. Hypertonic saline has been claimed to be effective but has the risk of coagulation failure and hypernatremia. Scant clinical data is available in India on the use of urea as an abortifacient.

The safety and efficacy of prostaglandins and their analogues for the termination of midtrimester pregnancy has been established by WHO Task Force on Prostaglandin. However, in order to evaluate their safety in the context of conditions existing in our country, multicentric studies were undertaken at centres attached to teaching hospitals. One trial compared the use of single shot intra-amniotic 50 mg $\text{PGF}_{2\alpha}$ and 2.5 mg 15(S)15-methyl $\text{PGF}_{2\alpha}$ for termination of pregnancy between 15-20 weeks. The second trial was the administration of a single shot extra-amniotic 0.92 mg 15(S)15-methyl $\text{PGF}_{2\alpha}$ for termination of pregnancy between 10-20 weeks.

Intra-amniotic route: A total of 885 women were enrolled in the first trial, of which 430 women had $\text{PGF}_{2\alpha}$ and 455 had 15-methyl $\text{PGF}_{2\alpha}$. Success rate at the end of 48 hours was 88.1 per cent (379 women) with $\text{PGF}_{2\alpha}$ and 93.0 per cent (423 women) with 15-methyl $\text{PGF}_{2\alpha}$. Mean induction-abortion interval with $\text{PGF}_{2\alpha}$ was 19.2 hours and with 15-methyl $\text{PGF}_{2\alpha}$ it was 19.3 hours. Abortion was complete in 48.8 per cent (185 women) with $\text{PGF}_{2\alpha}$ and in 56 per cent (237 women) with 15-methyl $\text{PGF}_{2\alpha}$. Vomiting was reported in 42.9 - 45.3 per cent cases and diarrhoea was reported by 24 per cent cases in the two groups.

Extra-amniotic route: In the second trial, a total of 1,648 women were given extra-amniotic 15(S)15-methyl $\text{PGF}_{2\alpha}$ and 1,225 (78.1 per cent) women aborted within 36 hours. Mean induction-abortion interval was 14.8 hours. Abor-

tion was complete in 282 (23 per cent) women, incomplete in 582 (47.5 per cent) women. Incidence of vomiting was 36.5 per cent and diarrhoea 33.7 per cent. Cervical injury was reported in 0.6 per cent women.

Vaginal route: Prostaglandin vaginal suppository is an alternate to intra-amniotic and extra-amniotic administration of prostaglandins for the termination of midtrimester pregnancy. The vaginal route has the advantage of being simple and the drug can be self administered. This approach could, therefore, be used at non-teaching hospitals and even at the primary health centre level. In order to evaluate the efficacy and safety of this approach, vaginal suppositories containing 3 mg 15-methyl PGF_{2α} methyl ester were used for the termination of pregnancy between 10-20 weeks of gestation in 288 women. Of these 79.2 per cent women aborted within 30 hours. Mean induction-abortion interval was 14.7 hours. Abortion was complete in 133 (58.3 per cent) women. Incidence of vomiting was 72.3 per cent and diarrhoea 76.8 per cent; cervical injury was reported in one woman. These trials are in progress.

Ethacridine lactate:

Alternate approaches for terminating second trimester pregnancy include intra/extra-amniotic instillation of solutions containing prostaglandins, hypertonic saline, urea, *etc.* While the safety and efficacy of some of these is still not established, the expense and non-availability deters the use of others. A clinical trial for assessing the safety and efficacy of ethacridine lactate was, therefore, undertaken since this preparation is apparently inexpensive and more readily available within the country.

Although several clinical trials to terminate pregnancy between 12-20 weeks with ethacridine lactate and ethacridine lactate in combination with oxytocics have been reported, it was difficult to interpret and compare clinical events as data of these trials were not collected in an identical manner. Different strengths, combination of drugs, time period of catheter in position, *etc.* were used. In order to evaluate the safety and efficacy of ethacridine lactate alone or in combination with spartine sulphate, a study was undertaken in a few centres. Analysis of the data in 386 women revealed that ethacridine lactate alone and/or in combination with spartine sulphate was safe and effective in terminating approximately 70 per cent pregnan-

cies between 12-20 weeks in 48 hours. This was comparable to the extra-amniotic prostaglandin approach and was inferior to intra-amniotic prostaglandins.

The cumulative success at the end of 24 hours with ethacridine lactate was only 32.3 per cent compared to 69 per cent with extra-amniotic prostaglandin and intra-amniotic PGF_{2α}. With intra-amniotic 15-methyl PGF_{2α} it was 74.9 per cent.

The mean induction-abortion interval with extra-amniotic 15-methyl PGF_{2α} was 14.8 hours, with intra-amniotic PGF_{2α} it was 19.2 hours and with intra-amniotic 15-S-methyl PGF_{2α} it was 19.3 hours. With ethacridine lactate alone it was 26.3 hours and in combination with spartine sulphate it was 26.7 hours. The most common side effects with prostaglandin *viz.* vomiting and diarrhoea were markedly less noticeable with ethacridine lactate. Complete abortions were 69.3 per cent with ethacridine lactate and in combination with spartine sulphate 59.6 per cent. With extra-amniotic 15-S-methyl PGF_{2α} only 31.8 per cent women aborted completely and with intra-amniotic PGF_{2α} it was 80 per cent and with 15-methyl PGF_{2α} it was 75 per cent.

Presently, prostaglandins are not available in India and storage as well as transportation may pose problems although development of newer analogues may overcome this especially as is the case with vaginal suppository.

The other alternative to terminate mid-trimester pregnancy is intrauterine saline. The success rate with saline as reported by various investigators was about 85 per cent at the end of 48 hours and 90 per cent at 72 hours with 66 per cent complete abortion. The mean induction-abortion interval was approximately 30 hours. Hypertonic saline is known for the added risk of coagulation failure and hypernatremia. Deaths have been reported in cases where abortion was induced with hypertonic saline. Furthermore, intra-amniotic instillation is difficult in 12-15 weeks pregnancy. Except for rigor (7.5 per cent approximately) no adverse effects with ethacridine lactate were noted and contraindications for the use of ethacridine lactate are very few. Low cost is an advantage as also the bactericidal property of ethacridine lactate. This drug has now been recommended for marketing and use for terminating pregnancies.

Isapgol cervical dilators:

Many centres in the country today use bougies and laminaria tents as cervical dilators for inducing abortions. Laminaria tents made of sea weeds are being imported at present and are expensive. Furthermore, their availability within the country is restricted. CDRI, Lucknow has succeeded in developing a cervical dilator from *Isapgol* (*Plantago ovata*). The cost of this dilator is fifty times lower as compared to the imported dilator. Limited studies have indicated that these dilators are effective and induce 10 mm dilatation within 8 hours. Further studies with these and bougies are in progress.

APPLICATION ORIENTED BASIC RESEARCH

MALE REPRODUCTION

Studies on Inhibin:

It is known that FSH is concerned with spermatogenic function and LH in that of testosterone production. Selective inhibition of FSH would, therefore, be one of the possibilities of inhibiting spermatogenesis without affecting androgen production. Investigations carried out at the Council's Institute for Research in Reproduction, Bombay, have revealed that testis has two non-steroidal protein components, one of which inhibits FSH secretion and the other LH secretion. These components termed Inhibin have been isolated from ram testis and semi-purified. Studies are in progress to examine the species specificity of the FSH inhibiting moiety and its use in controlling fertility in the male.

A study has also been undertaken at the Central Drug Research Institute, Lucknow, with the objective to separate, purify and identify the principle from a suitable source and then subject it to biological standardization for its anti-FSH activity. Results so far indicate that an anti-FSH factor is present in the testis, which is most probably identical with Inhibin and it is possible to raise antibodies against this testicular factor. Further work is in progress.

Studies on prolactin:

Capacitation i.e. alteration in the membrane of a spermatozoa has to take place before it can fertilize the egg. Interference with capacitation could result in the reduction or nullification of the fertilizing potential of spermatozoa. As the sperm capa-

citates, there is a reduction in its binding capacity to substances like tetracycline. Recent studies at the IRR, Bombay, have revealed that prolactin affects the process of capacitation as indicated by alteration of tetracycline binding capacity of spermatozoa. It seems likely that prolactin, present in semen and cervical mucus, would play an important role in capacitation and the consequent fertilizing capacity of spermatozoa. Work is in progress to examine this possibility.

A study was undertaken at Sri Venkateswar University, Tirupati, to find out the site of production of prolactin and its effect along with other gonadotropins on the male reproductive system. Enzymatic activity patterns were studied in metabolic (brain, liver, muscle and kidney) and reproductive tissues (testes, seminal vesicles epididymis and prostate gland). It was noted that specific similarities of certain enzymatic patterns existed in the two groups of tissues. Enzymatic response of reproductive and non-reproductive tissues to the extraneous hormonal factors was also found to be identical. It was observed that the later phases of spermatogenesis which invariably involved maturation in the epididymis and seminal vesicles were under similar enzymatic control as that of the liver. Thus, the possibility of non-reproductive tissue mediating metabolic regulation of reproductive tissues opens up a new horizon in the relationship between reproductive and non-reproductive tissue enzymes at the molecular level.

Studies on testes and spermatogenesis:

A study is being undertaken at the Banaras Hindu University, Varanasi, with the objective of collecting basic information regarding inhibition of spermatogenesis in the male by immunological methods. There is paucity of information regarding the effect of intratesticular administration of specific antibodies. This study provides a method for germ cell destruction by specific antibodies, bypassing the blood-testis barrier. It also provides control over the extent and duration of damage of the tubular epithelium and on the reversibility of spermatogenesis. Any possible interaction of the anti-testicular antibodies with other vital organs was avoided by intratesticular administration of the antibodies.

A study to comprehensively evaluate cases of oligo-azoospermia of undertermined origin by a battery of parameters, so as to identify

the pathophysiological mechanisms was undertaken. Preliminary results of the study ascertained the importance of testicular biopsy score count as a valuable tool for determining the state of spermatogenesis. The study further confirmed the observation, that the degree of spermatogenesis is inversely proportional to gonadotropic status. However, there is disagreement between these data and those reported by others which have shown that serum FSH is elevated in those cases where gametogenesis is arrested prior to spermatid differentiation. In this study, inspite of the absence of spermatids, serum FSH levels were in the normal range. Further work is in progress at the IRR, Bombay.

A study was undertaken at the Jawaharlal Institute of Postgraduate Medical Education and Research, Pondicherry, to find out the antifertility activity and reversibility of 5-thio-D-glucose, and to study its reaction on the glucose metabolism of the testes and other tissues. Preliminary data has shown that 5-thio-D-glucose acts as an antifertility agent in mice in a very low non-toxic dose. It is effective for testicular suppression only when taken orally whereas injections produce no activity. It inhibits testicular glucose metabolism. The effect is reversible if the drug is withdrawn.

Spermatozoa:

Since spermatozoa are stored in the epididymis for varying lengths of time in different species of mammals, a project was undertaken at Guru Nanak Dev University, Amritsar, to study several antiandrogens for their effect on this target organ. Four drugs namely Ovocyclin, chloromadinone acetate, clomiphene citrate and cyproterone acetate were investigated. With Ovocyclin, libido remained normal and the testis, and accessory reproductive organs were reduced in size. Epididymal ductules had normal epithelium but no sperms were seen. These atrophic changes were noted with chloromadinone acetate, clomiphene citrate and cyproterone acetate. It is proposed to extent this study to monkeys. Stereotoxic studies will also be included in this species.

A study has been undertaken at Banaras Hindu University, Varanasi, to understand the mechanism of maintenance of hydrolytic enzymes of spermatozoa in a latent form. This would enable to identify agents which may interfere with the fertilizing ability of sperms.

Studies on epididymis:

A project was carried out at the Institute of Experimental Medicine, Calcutta, to define hormonal mechanisms important in the biochemical control of gene expression in epididymis during sperm maturation. The assay of protein kinase from rat epididymal nuclei has been standardized. Work done so far indicated significant amount of protein kinase activity in epididymal nuclear extract. Further studies are in progress to purify the nuclear protein kinase.

Male accessory glands:

A study has been undertaken at Banaras Hindu University, Varanasi, to enable better understanding of the functional aspects of accessory organs in the male, including the relationship of spermatozoa of the mammalian species and accessory gland secretions. Histology and histochemistry of the accessory gland under normal condition and after administration of steroidal antiandrogen, cyproterone acetate, non-steroidal antiandrogen, N-phthalimide (DIMP), including sites of production and content of fructose, citric acid and sialic acid has been investigated in several species, including musk, shrew, Indian mongoose, bulls, rodents, etc. Investigations have revealed that there is diversity in the accessory glands even within closely related species. The study also emphasizes that species also differ with regard to the site of production and content of fructose, citric acid and sialic acid.

Adrenals:

Adrenocortical insufficiency results in lowering the activity of pyridoxal 5'-phosphate (PLP) dependent reactions like transaminase. These are reversed to normal when treated with steroids or fed additional B₆. To study the role of B₆ on the functions of the adrenals, male rats were kept on B₆ free diet and compared with pair fed B₆ added controls. The rats were sacrificed after a period of 10, 20 and 60 days. Results of this study at the St. John's Medical College, Bangalore, reveal a considerable decrease in ascorbic acid, RNA, total lipids, NEFA, hormonal secretions and a decrease in size of the gland, but an increase in ester cholesterol.

FEMALE REPRODUCTION

Gonadotropins:

Gonadotropins play a pivotal role in reproductive physiology and a better under-

standing of these processes would enable the development of better methods for the control of fertility. Considerable gaps exist in our knowledge on the regulation of gonadotropins; their synthesis; secretion; amount needed to initiate different physiological events; biochemical events initiated in the ovary and testis including the mechanism of their action at the molecular level; and disposal. In a project undertaken at the Indian Institute of Science, Bangalore, highly purified antisera have been prepared, and characterized for their specificity in terms of their ability to neutralize gonadotropins. Antibodies to gonadotropins have also been used to standardize radioimmunoassay procedures and also for using them as antagonists for studying gonadotropin action. This approach has helped in elucidating the mechanisms of action of FSH and LH at the cellular and molecular level. The model system used in the project initially was the laboratory rodent. During the last few years, a good primate colony has been built and emphasis is being switched to work on primates.

In addition to this, a major effort has been in the study of cyclical follicular maturation, termination of pregnancy and lactation. Homologous and heterologous gonadotropin antibodies have been used. Information accrued would help in the development of better methods for fertility control.

Ovary and oogenesis:

Allotransplantation of ovary was done in two human cases at the R.G. Kar Medical College, Calcutta. Prior to human studies experiments were performed in bitches and rabbits. Encouraged by the success, it is proposed to undertake transplantation of ovaries in more cases. In addition, all cases would be analyzed for their chromosome pattern, hormone status and immunological responses.

The cytological and histochemical studies of oogenesis in Swiss mice have been completed at the Berhampur University, Berhampur. Vacuoles were observed along the periphery of the ooplasm which dispersed as the oocyte matured. The vacuoles did not respond to any histochemical tests that were used. Further work is necessary on the oocytes as well as zona pellucida to draw conclusions regarding the role of these vacuoles in the maturation of oocyte.

The luteolytic effect of $\text{PGF}_{2\alpha}$ in almost

all laboratory animals including the non-human primate has now been unanimously accepted. However, the mechanism leading to luteolysis is still unsolved. Findings from a project undertaken at Raja Peary Mohan College, Uttarpara, Hooghly, West Bengal, have indicated that prolactin is capable of reversing the luteolytic effect of $\text{PGF}_{2\alpha}$ in the pregnant rat. Further, $\text{PGF}_{2\alpha}$ is known to stimulate follicular estrogen from the ovaries and this estrogen in turn exerts a consistent luteolytic effect by stimulating uterine $\text{PGF}_{2\alpha}$. In studies on the mechanism of action of estrogen, it has been shown that a concomitant regimen of progesterone or prolactin with estrogen is capable of reversing its luteolytic effect and could maintain normal pregnancy. It is proposed to further study the interaction between hormones of pregnancy and prostaglandins in sensitizing uterine component for initiating the sequences of labour. Understanding of such complicated physiology may help in manipulating the environment so that premature emptying of unwanted conceptus could be achieved.

Implantation:

One of the vulnerable areas in reproduction which can be easily interrupted is the implantation stage of pregnancy. Recent studies at the IRR, Bombay, have indicated that disruption of pregnancy in mice injected with antibodies to luteinizing hormone is associated with changes in the phosphatase activity in the early decidual cells. Studies are being extended to enzymes specific for implantation and their inhibitors.

In the ovary, the synthesis and release of steroid hormones is regulated by the pituitary hormones LH and FSH. There is no evidence to indicate that LH or HCG like material are present in the rabbit blastocyst and in pre-implantation embryo of mouse. It has been shown recently that these embryos contain steroid hormones and also the machinery to synthesize steroids. A study was, therefore, initiated at the All India Institute of Medical Sciences, New Delhi, to localise receptors or binding sites for LH and HCG in the morula and blastocyst stages of mouse embryos. Using indirect immunocytochemical techniques, it was shown that mouse embryos contained binding sites for LH and HCG but not beta sub-unit of HCG or FSH. It was also confirmed that the mouse blastocysts contain LH or HCG like material, using an immunoperoxidase technique. The presence of LH/HCG and its specific receptors in the morula and blastocyst is significant as

this opens up another important area where studies on regulation of steroid synthesis in the preimplantation embryo can be used for fertility control.

Pregnancy:

A project was undertaken at the K.G. Medical College, Lucknow, to evaluate biochemical imbalance associated with the frequent serious condition of toxæmias of pregnancy (pre-eclampsia). On the basis of work done till now it has been shown that 5-hydroxytryptamine levels are consistently increased in toxæmic cases as compared to normal cases. Further, in parallel with the above observation, the MAO activity in toxæmic cases is consistently lower than that in the normal, accounting for the increased 5-hydroxytryptamine level. Another observation is that there appears to be a shift in the localization of activity between the normal and the toxæmic tissues in as much as toxæmic tissues show pronounced MAO activity in the nuclear fraction as compared to the normal tissue where the major activity resides in the mitochondrial fraction. Further work is in progress.

NATIONAL PITUITARY AGENCY

Advances made in the field of protein chemistry have enabled scientists to extract and purify various hormones which the anterior pituitary secretes. The availability of these purified hormones and the development of sensitive techniques to detect, assay and characterize these, has triggered and facilitated research in understanding the role pituitary hormones play in the maintenance of normal body functions. The possibilities of estimating nano and even pico grams of the potent pituitary hormones has opened up new vistas for research which have enabled the understanding of the basis of metabolic and reproductive disorders and the way of treating these. The availability of pure hormones from the pituitary and development of sensitive techniques to estimate them has made a new breakthrough in the regulation of fertility in man and in animals of economic importance to him. The availability of pure preparations of pituitary hormones and antisera specific to them has enabled man to get an insight into how these hormones control the release of gametes, fertilization and implantation.

With a view to have a central agency which will provide purified hormones and reagents necessary for assays, a National Pituitary Agency has been established at the Insti-

tute for Research in Reproduction, Bombay. The major efforts of the agency are to collect human pituitaries on a national basis; establish national standards for pituitary hormones and reagents for RIA and their distribution to different workers in India; provide growth hormones and gonadotropins for therapeutic use; and improve the existing methodology of RIAs and organize training courses in RIA methodology.

It is heartening to report that during the short period since its establishment, growth hormone has already been isolated, purified and characterized. FSH, LH, prolactin and TSH should become available shortly.

DEVELOPMENTAL RESEARCH

The development and standardization of methods to detect and assay biologically active constituents present in vital organs, tissues or their products, is an important facet of research in reproduction and fertility control. Some of the newer developments are:

An enzyme immunoassay for human chorionic gonadotropin:

Hormone analysis, a procedure requiring extensive purification of the sample and great technical skill, has been relatively simplified by the use of radioimmunoassays. These specific, sensitive assay procedures, though exacting to carry out, are currently being used all over the world for routine estimation of HCG. In a developing country, however, the difficulty of getting suitable radio-active isotopes and the costly sophisticated equipment needed for performing these assays are the major limiting factors, even in fairly well-equipped research institutes and hospitals, leave alone smaller district hospitals. Therefore, the possibility was explored to develop alternative assays. In recent years, enzyme immunoassays are being developed for the sensitive estimation of hormones. The assays operate on the principle of RIA, but with the difference that only stable enzymes and less sophisticated equipment are used for their execution. Attempts were made to develop such an enzyme immunoassay for the estimation of HCG and to evaluate whether the assay so developed would prove as sensitive as the RIA assay for HCG. An enzyme immunoassay for HCG using alkaline phosphatase as a label has now been standardized. Future programmes envisage the use of a locally available high turn over enzyme and the development of assays for as many hormones as possible.

Haemagglutination inhibition technique for the detection and assay of HPL:

Decrease in HPL prematurely, spells danger to the foetus. A haemagglutination inhibition immunoassay method, which is simple and can be used even for routine testing in small hospitals has been developed for the assay of HPL for monitoring high risk pregnancies.

RIA kits for the estimation of HPL:

A highly sensitive radioimmunoassay kit for the estimation of HPL has been developed in collaboration with the Bhabha Atomic Research Centre, Bombay. A RIA kit for the detection and assay of insulin is expected to be ready soon.

Standardization of two new immunological parameters to detect immunity to spermatozoa:

Migration inhibition to detect CMI and a lymphocyte mediated antibody dependent cytotoxicity, both to human spermatozoa were developed and standardized. These procedures along with the others standardized at the IRR, Bombay, are employed for the detection and evaluation of the clinical significance of antibodies to spermatozoa.

An experimental model for studying effect of contraceptives on lactation:

Contraceptive steroids are being prescribed to lactating women. A number of these steroids which increase lactation, are also being considered for more widespread use in the family welfare programmes of developing countries. In view of conflicting reports available on their effect on the progeny, a systematic study is essential. The rat has been found to be an extremely good model to evaluate the growth, maturation, development and fertility of the progeny of mothers administered contraceptive drugs during lactation.

The sub-human primate as a model for contraceptive research:

Levels of reproductive hormone protein as well as steroid have been estimated in *Macaca radiata* (bonnet monkey) and *Presbytis entellus* (Langur monkey) with reference to the menstrual cycle in these two species. These basic data will prove of great value in determining whether or not to use these as experimental models for contraceptive research. The results

have indicated that both these species will prove invaluable in this respect.

Detection of chromosomal anomalies:

The Giemsa banding technique for identifying individual chromosomes for screening of metabolic diseases has been standardized. Methods to assay urinary aminoacids for the screening of certain metabolic disorders have also been standardized.

Pre-natal sex determination:

Attempts to detect sex prenatally have been highly successful. The sex of the foetus was determined accurately in over 98 per cent of the cases referred to the Institute.

Biodegradable polymers:

A project was undertaken by Sri Ram Institute, Delhi, in collaboration with IRR, Bombay, with a view to develop polymers based on lactic acid and glycolic acid and to study their biodegradable characteristics with reference to their application in the field of fertility control. Polymerization of lactic acid and glycolic acid has been done, and polymer samples containing 20 per cent w/w testosterone were studied for biodegradable and leaching rate for a period of 3 months. *In vitro* studies with norethisterone acetate and the polymer are in progress.

Synthesis of contraceptive steroids:

An effort is being made to make the country self-reliant with regard to the national demand for steroids which are being used for the preparation of oral contraceptive pills. This collaborative effort at Lucknow, Calcutta, Bangalore and Bombay, involves the total synthesis of 19 non-steroids (1-vinyltetralol from 6-methoxy-tetral-1-one, thiouranium salt from vinyltetralol, micro-biological reduction of secodione to secol, d-secol to d-pentenol, d-pentenol to d-tetraenol, tetraenol to estrone and norethisterone) and norgestrel.

Emphasis at the centre in Calcutta has been on the development of chemical process for the conversion of easily available vegetable raw-materials to 19 non-steroids in the total synthetic approach to the production of estrone and 19 non-steroids, 6-methoxy-tetral-1-one being the key intermediate. A technically feasible mechanical method has been developed and standardized where the preparation of this intermediate is initiated from

tetralin (available from petrochemicals and coal tar products) and involves sulphonation, alkali fusion and methylation followed by oxidation.

Similarly, other chemical methodologies for partial synthesis of 19 non-steroids based on vegetable raw materials have resulted in substantial development on a laboratory scale. The conversion of 16-dehydropregnenelone acetate to 19-methyl group and also androstan-17-one intermediate which has further 3 steps of transformation, would give rise to 19 non-

steroids for contraception. Fine intermediate organic chemicals and reagents required for this work have also been prepared through simpler methods.

At the collaborative centre in Bangalore the conversion of 16-dehydropregnenelone acetate (DHA) into dehydroepiandrosterone and DHA into dienone has been achieved.

It is proposed to continue this work and achieve the total synthesis of steroids.

ICMR NEWS

Dr. Shanta S. Rao, Director, Institute for Research in Reproduction, Bombay, participated in the meeting of the Steering Committee of the WHO Task Force on the 'Immunological Methods for Fertility Regulation' held at Geneva between 27th February and 2nd March, 1978.

Dr. A.D. Taskar, Chief Statistician, Indian Council of Medical Research, New Delhi, was a participant in the WHO Interregional Conference on 'Teaching Statistics to Medical Undergraduates' held at Karachi between 4th and 9th March, 1978.

Dr. C. Gopalan, Director-General, participated in the WHO Consultative meeting on 'Nutrition Programme Development' held at Geneva between 6th and 10th March, 1978 and in the workshop on the 'South East Asian Regional Programme for Applied Research in Malaria Control' held at New Delhi between 14th and 17th March, 1978.

Dr. S.B. Moodbidri, Research Officer, Institute for Research in Reproduction, Bombay, proceeded on a WHO Research Training fellowship for one year to U.K. and USA to study extraction and purification of gonadotropins.

ICMR AIDED SYMPOSIA/SEMINARS/WORKSHOPS

An International Symposium on 'Biomolecular structure, conformation, function and evolution' was organised at the University of Madras, between 4th and 7th January, 1978.

A workshop on 'Periodontology' was organised at the Dental College and Hospital, K.G. Medical College, Lucknow, from 9th to 13th January, 1978.

A workshop on 'Chemotherapy of leprosy' was organised at the Central Leprosy Teaching and Research Institute, Chingleput, on 21st January, 1978.

A workshop on 'Benefit through man-machine interaction' was organised by the Indian Association of Occupational Health and the Institution of Engineers (India) at Madras between 27th and 29th January, 1978.

Symposia on 'Family care - a learning situation', 'Health for all' and 'Human

fluorosis', were organised as part of 8th Annual Conference of the Indian Association of Preventive and Social Medicine, at the R.N.T. Medical College, Udaipur, between 9th and 11th February, 1978.

An International Symposium and a Workshop on 'Biomedical engineering' were organised at the Indian Institute of Technology, New Delhi, from 15th to 22nd February, 1978.

A workshop on 'Hospital infections with special reference to *Pseudomonas aeruginosa*' was organised by the Department of Microbiology, All India Institute of Medical Sciences, New Delhi, between 20th and 27th February, 1978.

A symposium on 'Environmental agents and their biological effects' is being organised at Osmania University, Hyderabad, in March, 1978.

A symposium on Leprosy is being organised at the V.M. Medical College, Sholapur on 25th and 26th March, 1978.

A workshop on 'Hydrocephalus' is being organised at the All India Institute of Medical Sciences, New Delhi, between 27th and 31st March, 1978.

A symposium on 'Anatomy in medical education' is being organised at the Department of Anatomy, All India Institute of Medical Sciences, New Delhi in April, 1978.

A laboratory teaching workshop in Physiology is being organised by the Department of Physiology, All India Institute of Medical Sciences, New Delhi, between 17th and 29th July, 1978.

A symposium on 'Clinical pharmacokinetics' is being organised during the V Southern Regional Conference of the Indian Pharmacological Society at Pondicherry on 9th and 10th September, 1978.

A symposium on 'Population structure and human variation' is being organised during the International Congress of Anthropological and Ethnological Sciences at Bombay between 19th and 21st December, 1978.

Symposia on 'Reproductive biology' and 'Nutrition' are being organised during the VII International Congress of the Primatological Society at the Indian Institute of Science, Bangalore between 1st and 5th January, 1979.

PROGRAMME OF SCIENTIFIC LECTURES AT THE INDIAN COUNCIL OF MEDICAL RESEARCH, NEW DELHI

Date	Topic	Speaker
3.3.1978	Indigenously developed electronic cardiac instruments	Surgeon Commander A.K. Deb, Bangalore.
17.3.1978	Endemic Fluorosis in Punjab (Basanti Devi Amir Chand Prize Oration 1978)	Dr. S.S. Jolly, Patiala
31.3.1978	Erythropoiesis in thyroid diseases	Dr. R.J. Dash, Chandigarh.
7.4.1978	Advances in the management of ischaemic heart disease (Chaturvedi Kalawati Jagmohan Dass Memorial Award Oration 1977)	Dr. K.K. Datey, Bombay.

COUNCIL'S TRAINING PROGRAMMES FOR 1978

Leprosy:

At the Central Jalma Institute for Leprosy, Agra.

Training course in Leprosy for medical officers: (December, 1978).

Virology:

At the Virus Research Centre, Poona.

(1) Diploma course in Virology of Poona University: (July, 1978).

- (2) *Training course for Technicians for a period of one year.
- (3) Short-term course in Animal Cell Tissue Culture: (June, 1978).

Reproductive Biology:

At the Institute for Research in Reproduction, Bombay.

- (1) Training course in Reproductive Biology: (January, 1978 to March, 1978).
- (2) Radioimmunoassay of Protein and Steroid Hormones: (January, 1978 to March, 1978).
- (3) Training course in Genetics: (January 16, 1978 to February 15, 1978).
- (4) Training course in Basic Immunology: (February, 1978 to March, 1978).
- (5) Training course in Contraceptive Research and Reproductive Endocrinology: (March, 1978).

Nutrition and Endocrinology:

At the National Institute of Nutrition, Hyderabad.

- (1) M.Sc. (Applied Nutrition) course: (June, 1978 to February, 1979).
- (2) Annual certificate course in Endocrinological Techniques and their Application: (October, 1978 to November, 1978).
- (3) Annual certificate course in Nutrition: (December, 1978 to February, 1979).

Haematology:

At the Blood Group Reference Centre, Bombay.

- (1) A certificate course in Blood Banking Technology and Basic Haematology for medical officers: (February 1, 1978 to March 31, 1978).
- (2) Training course in Blood Banking Methodology for Technicians: (May 2 to 14, 1978).

Occupational Health:

At the National Institute of Occupational Health, Ahmedabad.

- (1) *ICMR/WHO training course in Industrial Toxicology.
- (2) *Refresher course in Occupational Health for E.S.I. medical staff.
- (3) *Training course on Chemical Hazards in Chemical Industry organised jointly by the NIOH and the National Safety Council.

Clinical Pharmacology:

At the Department of Pharmacology, Seth G.S. Medical College, Bombay.

Training course in Clinical Pharmacology: (January 15, 1978 to February 28, 1978).

Biostatistics:

At the National Institute of Nutrition, Hyderabad.

Annual training course in Biostatistics for Statisticians: (November, 1978).

Laboratory Animal Technology:

- (1) At the Virus Research Centre, Poona.

Short-term course in Breeding and Maintenance of Laboratory Mouse Colonies: (March, 1978).

- (2) At the National Institute of Nutrition, Hyderabad.

Laboratory Animal Technicians Training Course: (August, 1978 to September, 1978).

COURSES FOR TALENT SEARCH SCHEME FELLOWS

Haematological Techniques:

- (1) At the Department of Pathology, Christian Medical College, Vellore: (February 28, 1978 to March 10, 1978).
- (2) At the Department of Haematology, Post-graduate Institute of Medical Education and Research, Chandigarh: (September, 1978).

Clinical Pharmacology:

At the Department of Pharmacology, Post-graduate Institute of Medical Education & Research, Chandigarh: (March 6 to 15, 1978).

*Clinical Chemistry and Medical Instrumentation:

At the National Institute of Nutrition, Hyderabad.

*Use of Radioisotopes in Medicine:

At the National Institute of Nutrition, Hyderabad.

*Cell-Biology and Cyto-Genetics:

At the Indian Institute of Science, Bangalore.

*Principles and Methods in Medical Statistics:

At the Tuberculosis Chemotherapy Centre, Madras.

*Methods used in Diagnostic Virology:

At the Virus Research Centre, Poona.

*Dates to be announced later.

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TECHNICAL REPORTS

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Research in Health Practices (1970)	4.00
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