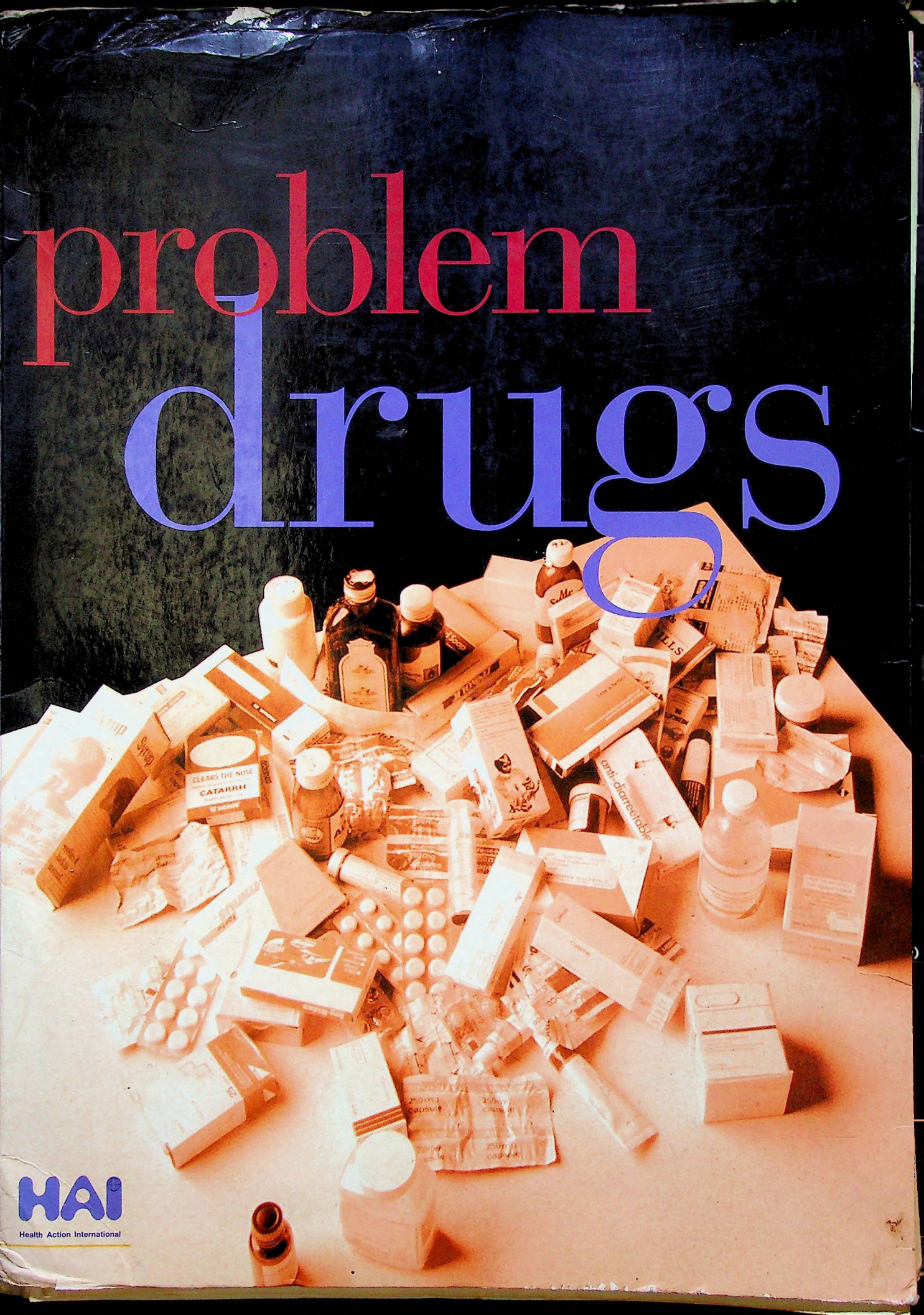
problem drugs



HAI
Health Action International

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problem drugs

How to use this pack

You can use the information in this pack to do four things:

- inform yourself
- inform others
- conduct local research
- campaign for change.

1. Inform yourself about the problems related to pharmaceuticals.

2. Inform others, such as local organisations, health workers, the media and government officials, by using the pack as the basis for news releases, articles, talks, exhibitions, meetings and discussions.

3. Conduct local research by selecting one or more of the categories of problem drugs and examining the situation in your community or country. Identify local health workers, pharmacists and/or pharmacologists who are willing to help with technical information. You could:

a) obtain a list of all the products on the market in one of the categories and compare them to the medicines described in the pack to see if they are appropriate;

b) use your local public library or a university or medical school library to check medical journals for promotion of inappropriate medicines similar to those described in this pack;

c) visit pharmacies and health care facilities to collect packages, package inserts and other information on drugs mentioned in this pack, and compare the information supplied. You could also conduct simple surveys on which drugs are recommended for common illnesses, such as diarrhoea or cough and colds.

4. Use the results of your research and the information in this pack to **campaign for change**. Call on government authorities, companies and health worker organisations to take action to improve the rational use of drugs in your area.

IMPORTANT NOTICE

Problem Drugs is not intended as a treatment guide. If you have any questions about a medicine you are taking as a result of reading this pack, please seek further information from a doctor, pharmacist or drug information service.

Abbreviations

AAMI	age associated memory impairment
ADDH	attention deficit disorder with hyperactivity
ADR	adverse drug reaction
AIDS	acquired immunodeficiency syndrome
AMA	American Medical Association
APMA	Australian Pharmaceutical Manufacturers Association
ARI	acute respiratory infections
ATH	Programme for Appropriate Health Care Technology (of the World Health Organization)
BGA	German drug regulatory authority
BMA	British Medical Association
BNF	British National Formulary
COC	combined oral contraceptive
CPMP	Committee for Proprietary Medicinal Products (of the European Community)
DDD	defined daily dose
DES	diethylstilboestrol
DMPA	depot medroxyprogesterone acetate (Depo-Provera – contraceptive)
DNA	deoxyribonucleic acid
DSM-III	Diagnostic and Statistical Manual of Mental Disorders
EC	European Community
EFPIA	European Federation of Pharmaceutical Industry Associations
EP	oestrogen-progesterone (drug)
FDA	Food and Drug Administration (of the USA)
HAI	Health Action International
HCG	human chorionic gonadotrophin
Hib	Haemophilus influenzae type b
HIV	human immunodeficiency virus
HMG	human menopausal gonadotrophin
HMO	health maintenance organisation
HRT	hormone replacement therapy
IAAAS	International Agranulocytosis and Aplastic Anemia Study
IDRC	International Development Research Centre (Canada)
IFPMA	International Federation of Pharmaceutical Manufacturers Associations
IKS	Swiss drug regulatory authority
IOCU	International Organization of Consumers Unions
ISIS-2	Second International Study of Infarct Survival
IU	international units (of vitamins)
IUD	intrauterine device (contraceptive)
MaLAM	Medical Lobby for Appropriate Marketing
MAOI	monoamine oxidase inhibitor
MBD	minimal brain dysfunction
MIRC	Market Intelligence Research Company
MRSA	methicillin-resistant Staphylococci aureus
MSD	Merck Sharp and Dohme
NCC	National Consumer Council (UK)
NCEs	new chemical entities
NEFARMA	Association of Dutch Pharmaceutical Industries
NET-OEN	norethisterone oenanthate (contraceptive)
NIH	National Institutes of Health (USA)
NSAIDs	non-steroidal anti-inflammatory drugs
ORS	oral rehydration solution
ORT	oral rehydration therapy
OTC	over-the-counter (drug)
PAHO	Pan American Health Organization
PID	pelvic inflammatory disease
PMT	premenstrual tension
POP	progestogen-only pill (contraceptive)
R&D	research and development
RDA	recommended daily allowance (of vitamins)
SIDA	Swedish International Development Authority
SMON	subacute myelo-optic neuropathy
STD	sexually transmitted disease
UNICEF	United Nations Children's Fund
UNESCO	United Nations Educational, Scientific and Cultural Organization
UNFPA	United Nations Population Fund
USAID	United States Agency for International Development
VHAI	Voluntary Health Association of India
WEMOS	Working Group on Health and Development Issues (Netherlands)
WHA	World Health Assembly
WHO	World Health Organization

Terminology

antibiotics	technically, antibiotics are only those substances produced by microbes. Thus, antibacterials or antimicrobials such as the sulphonamides, the quinolones, and trimethoprim are not strictly antibiotics. However, in this pack, the term antibiotic refers generally to all antibacterial and antimicrobial drugs.
billion	one thousand million (1,000,000,000)
dollar or $	US dollar

PUT THE PEOPLE OF YOUR CONSTITUENCY ABOVE PROFIT OR PRESSURE!

Fact Sheet for Policy Makers

- India is one of the cheapest countries for drugs. For e.g. Ranitidine costs Rs. 6 for 10 tablets in India but costs Rs. 74 in Pakistan and Rs. 864 in the USA!
- This was primarily because of the stance that India took of not allowing product patent, thereby creating a vibrant pharmaceutical industry in India
- In India there are 33 million diabetics, 20 million asthmatics, 4.5 million who suffer from tuberculosis, 2 million from malaria and 5.1 million HIV AIDS patients
- Low cost drugs are absolutely essential in a country like India where social/medical insurance is not available
- 80 Countries are depending on India for their life saving Medicines!

Impacts of the Proposed Patent Amendment Bill: -

- We have to adopt product patent as part of out TRIPS obligations, **but we do not have to adopt any measures beyond the TRIPS agreement**
- **The proposed amendment goes beyond the TRIPS agreement**
- Given that Product patents will have serious public health impacts, we need to be careful about the final amendment
- **Government would soon spend 10 times that of the current expenses meeting public health and employee's drug needs if the present Amendment bill is passed**

Note for instance the impact on

1. **Drug Prices**

- With Product patents, there is an absolute monopoly that is given to the owners of the patent, which also means the absolute ability to control the price of the drug
    - Patients suffering from Chronic Myeloid Leukemia (CML), a life threatening form of cancer use an **effective drug called Gleevec** (sold by Novartis AG), is costing Rs. 1,20,000 while the generic versions are available at Rs. 9,000-12,000 per month. However, the EMR granted to Gleevec is threatening the supply of generic drug.
    - 4 years back HIV / AIDS drugs costed Rs. 4,50,000 per year but because of Indian patent laws the same is now available at Rs. 7,500 per year! But these drugs could go back to Rs. 4,50,000 once the Amendment is passed.
    - **A court case was won in South Africa to allow cheaper HIV / AIDS drugs from India. But our government does not want to listen to this.**

2. **Argument of multinational Pharmaceutical companies**

- The larger Pharmaceutical companies claim that they need strong patent protection because of the high costs involved in developing a new drug. But let the facts speak for themselves
    - i. **Majority of Pharmaceutical spending is on marketing (35 %) compared to R & D (14%)**
    - ii. **Of the 14 % spent on R & D, the bulk is on non essential drugs like Viagra etc**
    - iii. **Much of R &D efforts are for new uses of old drugs rather than new drugs**
- Finally very little is spent on R & D for new, essential drugs.
- SO THE BILL SUBSIDISES THE MARKETING AND OTHER PROFIT MAKING COSTS OF PHARMA COMPANIES WHEN THERE IS A GREATER OBLIGATION TO PROTECT PEOPLE'S HEALTH

THE PRESENT GOVERNMENT PLANS A PRESIDENTIAL ORDINANCE ON SUCH AN IMPORTANT ISSUE OF PUBLIC HEALTH INSTEAD OF A DEBATE IN THE PARLIAMENT!!!

- Your people

PUT THE PEOPLE OF YOUR CONSTITUENCY ABOVE PROFIT OR PRESSURE!

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PRICES OF MEDICINES WILL SOON RISE-
ACT NOW OR PAY LATER!!

AFFORDABLEMEDICINES AND TREATMENT CAMPAIGN (AMTC)

Four years ago, millions of people living with HIV/AIDS could not afford the price of antiretroviral (ARV) drugs. The price was between US$10,000 –12,000 (Approx.Rs.4,50,000 – 5,40,000) per annum. By 2003 the prices had come down to US$ 140 (Rs.6300) per annum. How did this miracle happen? The answer lies in the Indian Patents Act, which provides only process patent protection to pharmaceutical inventions. However, after 31st December 2004, one cannot expect a repetition of this miracle because India will have to change its patent law and most of the new medicines will become just as costly as *gleevec*.

Gleevec the most effective anti-cancer drug cost Rs. 1, 20, 000 per month while the generic version is available less than one tenth of *gleevec*. An exclusive marketing rights for gleevec threatens the supply of generic drugs in India.

Act now to keep medicine costs low!

What is a Patent?

A patent is a limited monopoly given to individuals/corporations for a limited number of years for technological inventions /innovations by preventing others from using the patented technology. It is granted at the request of individuals/ corporations by the Patent Office in respective countries. Hence, the patent right is available within the territory of the granting countries. Nearly 97% of the world's patents belong to developed countries. Broadly patents can be classified into process patent and product patent. A process patent means that the monopoly is on the process of manufacturing the product and not on the product per se. On the other hand, the product patent gives a monopoly on the product itself that prevents others to manufacture, sell, distribute and import the patented product without the authorisation of the patent holder. Hence, a product patent on drugs means that only the patent holder can produce the patented drug in the normal circumstances. Monopoly as a rule results in high price and put the patented drug out of reach of majority of the people in India. On the other hand computation results in low price.

For instance, till 2001 Antiretroviral (ARV) drugs, the only effective treatment for HIV/AIDS, used to cost US$12000 per annum. The Indian drug companies, using the non-availability of product patent in India, could bring down the price to US$140 per annum within three years of their entry into the market. In 2001, the mere announcement of availability of a generic drug forced the multinational Merck to cut down the price of its ARV to US$800 per annum. Presently the generic companies supply these drugs at $140 per annum.

The Future Scenario

Right now, the Indian Patents Act provides only process patents for inventions in the pharmaceutical sector. As a result, more than one person is allowed to make the same drug provided they use different process to make their version of the product (if the process is protected by patent). Further, till 2002, the term of patents for pharmaceutical inventions was only seven years. These two factors enabled competition in the market by permitting more than one producer to produce the same drug. This resulted in the phenomenal growth of pharmaceutical industry in India and increased availability and accessibility of drugs. As a result drugs are available in India at world's lowest price.

However, India must amend its Patent Act by 31 December 2004 to introduce product patent regime to comply with Trade Related Aspects of Intellectual Property Rights (TRIPS). TRIPS is part of the Final Act of Uruguay Round, which established the World Trade Organisation (WTO). India signed the TRIPS Agreement to become a member of the WTO in 1994.

The TRIPS Agreement prescribes universal minimum standards for seven types of intellectual property rights, including patents. There is a time line for implementation of obligations under the TRIPS Agreement. India amended its Patents Act in 1999 and 2002 to incorporate changes within the Patents Act to comply with the TRIPS Agreement. These changes include extension of patent protection to microorganisms, extension of the term of the patent protection, introduction of exclusive marketing rights for drugs and agro-chemicals, etc. According to the TRIPS Agreement developing countries like India should extend product patent protection to pharmaceuticals and agro-chemicals on or before 1 January 2005. Government is hurriedly trying to introduce an amendment bill in the winter session of the Parliament (December 2004). The present government has adopted the same bill introduced by the previous NDA government.

After the introduction of product patent protection only the patent holder or any authorised person through license can produce the patented drug during the lifetime of the patent. As a result, there would be only one manufacturer producing and distributing the patented product Introduction of product patents means that drug companies in the normal course come out with generic will not be able to do so until the expiry of 20 years of patented life. Further, the implementation of product patents cover all drugs patented on or after 1 January 1995. Hence, the product patent regime reduces the access to many new drugs and compromises the right to health. The impact of product patent in India will not be visible immediately. However, the product patent will reduce the access to new medicines.

Is There a Way?

Yes, certain measures can be incorporated on the Patents Act to ensure accessibility and availability of drugs. India can safeguard its interest by using the manoeuvring space available within the TRIPS Agreement. India has used some of these measures in the last two amendments to the Patents Act safeguard the public interest. However, measures have not been used at the optimum level to take maximum leverage. The main issues with the present amendment bill are:

Patentability

The first step in this direction would be to deny usage and dosage patents. Contrary to popular perception, there are many patents on a single drug mainly on their usage and dosage forms. Such multiple patents on a single drug will extend the monopoly beyond the expiry of original patent. A study shows that out of 1035 new drugs approved by the US regulatory authority during 1989-2000 only 35% contains a new chemical entity. However, the bill proposes to provide patents to new use of known medicines.

Compulsory License

A second step would be a total revamp of the compulsory licensing system. The present compulsory license regime in the Patents Act is loaded with cumbersome procedural formalities with no fixed time line. Fulfilment of these formalities itself delays the granting of compulsory licensing unreasonably and reduces the compulsory license to an ineffective mechanism to check monopoly.

Pre-grant Opposition

The bill proposes to do away with the pre-grant opposition procedure. Pre-grant opposition gives the public to challenge the patent application before the grant of patents. Therefore it is absolutely necessary to block the trivial patents.

- **PUT RIGHT TO HEALTH ABOVE PATENTS**
- **SAY NO TO USAGE & DOSAGE PATENTS**
- **RETAIN PRE-GRANT OPPOSITION**
- **SAY NO TO TRIPS PLUS PROVISIONS**

Other Required Amendments

- New definition for invention
- Changes in the non patentable invention
- Strengthen parallel importation
- No change in the pre grant opposition
- Introduce non voluntary license
- Introduce ceiling on royalty
- Strengthen local working requirements

For more details contact:

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Email: amtc_india@yahoo.co.in

Act Up-Paris Press release – Monday December 6
Act Up-Paris had an action earlier today at the Indian Embassy. Pictures are on the web site They transmitted the sign on letter to the secretary of the Ambassador. A meeting should be schedule later in the week.
GaL
http://www.actupparis.org/portfolio2.php?id_document=1510

Global access to medicines is threatened
The Indian government must postpone amending its patent law

Today December 6 2004, French aids activist group Act Up-Paris demonstrated in front of the Indian consulate in Paris to protest against Indian Industry Minister Mr Kamal Nath, whose recent policies are threatening global access to generic medicines. Photographs are available on www.actupparis.org

Minister Nath has announced a revision of the Indian Patents Act aiming at putting India in compliance with its WTO obligations. But Mr Nath, giving in to pressure from Washington and Western pharmaceutical companies, is proposing amendments which, if enacted, will block the manufacture and export of cheap generic drugs to AIDS-ridden countries in Africa and Asia .

Starting January 1st, the WTO expects India to grant patent monopolies on medicines to international drug companies. But India plays a unique role in global access to medicines. According to WHO, India is the world's chief exporter of cheap generic drugs – primarily to poor nations in Africa and Asia that have no pharmaceutical capability of their own.

Due to the WTO patent process, several generics have already had to be withdrawn from Indian pharmacies, such as the generic version of anti-cancer blockbuster Gleevec, which the patent owner is selling at 57 000 dollars. Early next year, the top-selling HIV drug Combivir is expected to undergo patent protection too, even though UN agencies estimates that up to 30% of African AIDS patients receiving treatment now are using one of the Indian generics of Combivir, such as Cipla's Duovir or Ranbaxy's Avocom.

In this context, the survival of millions of indigent people with HIV rests on India's continued ability to make and export cheap generic versions of new, effective HIV treatments. In 2001, the WTO recognized developing countries's right to circumvent drug patents through a mechanism known as « compulsory licensing ». Yet Minister Nath intends to rig India's compulsory licensing system with unlimited injunctive relief appeals that the WTO doesn't mandate, and that the drug companies have used to stifle the issuance of any license.

The activists from Affordable Medicines Treatment Campaign in India, as well as Health GAP in the US and Act Up in France, demand that Mr Nath implement a strictly enforceable deadline of one to three months for the review of a compulsory license request, as well as the withdrawal of injunctive relief in drug company's rights of appeal. Activists also stress that nothing is forcing India to amend its patent law in haste : most other developing countries have managed to exceed the deadlines set by WTO for complying with its patent norms.

Tomorrow Tuesday December 7, Affordable Medicines Treatment Campaign organizes a march on Parliament in Delhi to request its amendments be passed.

OPPOSE PATENT (AMENDMENT) BILL---WHY?

1. The Bill totally ignores the flexibility available within the Agreement on Trade Related Aspects of Intellectual Property Rights (TRIPS) and compromises accessibility and availability of medicines, agrochemicals, seeds, pesticides, etc. If the bill in its present form becomes law, it will seriously compromise the right to food and health.

2. The Bill proposes to extend the scope of patentability beyond the TRIPS requirements by amending Section 3(d) of the Patents Act to provide patents to new use of known medicines. There is no obligation under TRIPS to provide a patent to either new use or new dosage of known medicines. The product patent should be given only to new chemical entities and not to either new use or dosage forms or any other forms of known molecules. This will limit the number of patent protected drugs.

3. The Bill proposes to do away with the pre-grant opposition procedure. Currently, there are approximately 6000 applications pending in the mailbox protection. In the absence of pre-grant opposition, these 6000 applications would escape public scrutiny. Public scrutiny is crucial in light of the fact that less than 500 drugs have been granted marketing approvals in India between 1995-2004. Hence, pre-grant opposition is absolutely essential for blocking trivial patents. It is also part of natural justice to give an opportunity to interested parties, including civil society, to be heard before granting a monopoly.

4. The Bill has not properly incorporated the August 30th Decision of the TRIPS General Council, which permits the grant of compulsory licenses for export purpose to countries with no or insufficient manufacturing capacity in the pharmaceutical sector. The Bill proposes to permit compulsory licensing to a country with no or insufficient manufacturing capacity in the pharmaceutical sector if there is a corresponding patent in the importing country. This ignores the fact that in many instances, there may not be any patent protection in the importing country because the deadline for Least Developing Countries (LDCs) to comply with TRIPS is 2016. In this case, the Indian drug companies would not be able to export to LDCs in the absence of a compulsory license granted by the LDC.

5. Lastly, the compulsory license regime within the present Patents Act contains cumbersome procedures without any time line for the final disposal of the application. This renders the compulsory license system ineffective to curb abuse of patents because procedural requirements take away the deterrent element of the compulsory license mechanism.

6. The other safeguards in the present Patent Act, e.g. parallel importation, Bolar provision, and experimental exception, should be amended to make use of the TRIPS flexibility in its full extent.

Patent & Access to Medicines

Anand Grover
Lawyers Collective HIV/AIDS Unit

What is a Patent?

- A monopoly given for limited years for inventions
- Available for products and process Available in a territory, country, economic union,
- Prevents another party without consent from (making), using, offering for sale, selling, importing the **product or the process**

Patent: Implications?

Patent granted by the Patent Controller

- Only single manufacturer in the normal course
- Monopoly
- No competition
- High prices
- Compromises accessibility & availability
- e.g : ARV Drug

No Patent granted

- More than one manufacturer
- Competition
- Lower prices
- Availability and accessibility increased

Indian Patents Act 1970

- No product patent for drugs or chemicals
- Process patents only protected
- Protection only for only seven years
- Result: No monopoly in products
- More than one manufacturer
- Enabled competition
- Drugs are available at the lowest prices in the world
- Compulsory Licenses to facilitate availability & accesibility

TRIPS Patent Regime

- Trade Related Aspects of Intellectual Property
- Copyright, Trademarks, Geographical Indications, Industrial Designs, Patents, Layout designs of ICs, Undisclosed Information, Anti-Competitive Practices
- Laws have to be enacted in each signatory country for protection of Intellectual Property
- India is a signatory
- Came into force on 1st January 1995
- Applicable to inventions after 1st January 1995
- Time period given for sets of countries to comply
- India to comply with TRIPS by 31st December 2004

TRIPS Patent Regime

- Lays down minimum conditions for compliance
- Allows for flexibility
- **Patentable**: Invention which is new, involve an inventive step and capable of industrial application, Excludes patenting of plants and animals, except microorganisms and varieties of plants
- **Type of Protection**: For Products and Processes
- **Period of Protection**. Minimum 20 years for both
- **Interim period 1995 to 2004**. Provide for Exclusive Marketing Rights
- **Minimum conditions** for granting of compulsory license: Consent, Judicial Review, Limiting Period
- **CL**. Consent not required in cases of national emergency, extreme urgency, non-commercial public use, anti-competitive practices

TRIPS compliance in India

- India has not used the flexibility in TRIPS
- Already partially complied by 1999 and 2002 amendments
- **Patentable**: Invention of a product or process which is new, involves an inventive step (not obvious to person skilled in the art) and capable of industrial application; Excludes patenting of plants and animals except microorganisms. Special law for plant varieties
- **Type of Protection**: Provided for Products and Processes
- **Period**: Provided 20 years for both
- **Interim period 1995 to 2004**: Provided for Exclusive Marketing Rights after Dispute Panel decision
- **Compulsory Licenses:** Reasonable requirements of the public. Not available at reasonably affordable prices, invention not worked in India
- Compulsory Licensing **procedures** very cumbersome

3rd Bill: New Use

Section 3 excludes patentability of-

- Invention which is frivolous or obvious
- *Mere* discovery of scientific principle
- Discovery of a living thing or non-living substance occurring in nature
- *Mere* discovery of a new property
- Discovery of **(mere)** new use of a known substance
- Substance derived from a mere admixture of existing substances

The word mere will result in endless litigation. It needs to be deleted from all of Section 3

Grant of Patent: Extant Procedure

Examination and Publication

- To check for patentability and exclusion
- Application is complete with specifications
- Check for anticipated publications
- Check for prior claims: Assign Priority date
- Acceptance complete specification
- Publication of complete specification
- On publication the applicant has rights of patent holder but cannot sue for infringement

Pre-Grant Opposition: Procedure

On publication of acceptance of complete specification any person may oppose on the ground that the invention :-

- has been wrongfully obtained
- has been published before the priority date claimed
- claimed is in the public domain
- does not involve an inventive step or is not patentable
- has been anticipated by local community knowledge

There is another application with an earlier priority date

Oppositionist is entitled to be a party to the patent grant proceedings

Pre- Grant Opposition: 3rd Bill

Applicant may be granted a patent by the Patent Controller Chapter VIII

Patent can be revoked by the High Court on many more grounds

Pre-grant limited to

- Patentability: novelty, inventive step, industrial application
- Non-disclosure/ wrongful information given relating to source or geographical origin of the biological material or anticipation of local or community knowledge

Oppositionist is not entitled to be a party to the patent proceedings

Patent applicant has rights to patent holder on publication of application but can sue only of grant of patent, retrospectively

Compulsory Licensing: 3rd Bill

There is no change of CL procedure still cumbersome

Compulsory License can be granted only if the country to which the product is being exported is the without or insufficient manufacturing capacity and has granted a compulsory license for that product

Most countries without or insufficient manufacturing capacity are LDCs which do not have patent regimes. Therefore they have no law for granting of CLs

EMR ON GLEEVEC

- 25,000 cancer patients per year suffer from Chronic Myeloid Leukemia annually
- β-crystalline form of "Imatinib mesylate" available for treatment of CML
- 2003: Novartis's Branded version of Imatinib mesylate "Gleevec" priced at: Rs 120,000 (USD 2400) per month per person.
- 2003: Generic versions available at Rs. 8,500 (170USD) to 12,600 (252 USD) per month.

EMR ON GLEEVEC

- ***April 1992 (Switzerland):*** **Original patent application claiming wide spectrum compounds including salts**
- ***July 1997 (Switzerland):*** **Subsequent patent application (1764/97) claiming β-crystalline form of the salt.**
- ***July 1998 (Australia):*** **Subsequent application filed claiming priority from '97 Swiss application**
- ***13.08.2001 (Australia):*** **Marketing approval granted**
- ***28.02.2002(Australia):*** **Patent granted**
- ***4.12.2001 (India):*** **Marketing approval granted**
- ***March 2002 (India):*** **EMR application filed using grant of Australian patent application and marketing approval**
- ***10 December 2003 (India):*** **EMR granted to Novartis for Gleevec containing Imatinib Mesylate**

EMR ON GLEEVEC

- Original patent is PRE-1995 (not patentable)
- Subsequent application is not patentable [S.3(d) &(e), *Patents Act, 1970*]
- EMR granted in India on the basis of grant of patent and marketing approval in Australia
- ***EFFECTS:***
  - High Court injunction against six generic drug manufacturers
  - Suit pending against the lone generic manufacturer presently producing generic version of Gleevec
  - Access denied to 25,000 CML patients annually

Chetley, A. *Problem Drugs*, Amsterdam,
Health Action International, 1993

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Tales of dependence

Tess Higham went to her doctor suffering from exhaustion and anxiety. The doctor prescribed antidepressants and sleeping tablets. This prescription began a dependency on psychotropic drugs that lasted for 21 years. The last five years of this period she was on triazolam (Halcion). She says: "I have lost 21 years of my life by being on drugs and the last five were the worst while I was on Halcion. I have forgotten many things and feel that I have undergone chemical lobotomy."[1]

Peter Ritson was working in a hot climate for some time and found it difficult to sleep. He was prescribed a benzodiazepine tranquilliser to take every night. That was the start of a 12-year addiction to the drug, an addiction that took him two years to recover from.[2]

Psychotropic drugs are powerful agents of mood change. All carry some risk of side effects and in many cases give rise to psychological or physiological dependence. They can also be dangerous in overdose.

There are four main types of psychotropics:
- hypnotics, used to treat sleeping problems;
- tranquillisers or anxiolytics, used to treat anxiety;
- antidepressants, used to treat depression; and
- antipsychotics, used to treat the major psychoses.

The box on page 184 lists some of the many drugs in each of these categories.

The global market for psychotropic drugs was worth $4.4 billion in 1991, and is expected to reach $7.6 billion by 1996.[3] Table 10A-1 gives the breakdown of sales according to the main types of drugs. The US market alone was estimated at $3.3 billion in 1991 and is expected to reach $6.4 billion by 1997. Psychotropic drug prescriptions represent nearly 20% of total prescriptions in the USA.[4]

Table 10A-1
World Market for Psychotropic Drugs (1991)

Therapeutic type	World Sales 1991 $ Million
Hypnotics	406
Anti-anxiety drugs	1,200
Antidepressants	1,500
Antipsychotics*	1,244
Total	**4,350**

* includes anti-epileptics and drugs to treat Parkinson's disease

Source: FIND/SVP, *The Market for Psychotropic Drugs*, New York, FIND/SVP, 1992, cited in: Anon., "Psychotropic sales $7.6 bill by 1996?", *Scrip*, No 1720, 22 May 1992, p26

The growth of addiction: barbiturates

The early history of drugs to treat anxiety and sleep disorders set out a pattern of addiction that continues today. One drug after another was introduced as the safe replacement for an addictive drug, only to prove in time also to be addictive. First it was alcohol and opium; then morphine, cocaine and heroin; then chloral, bromides and barbiturates; through into benzodiazepines and their most recent replacements.[5]

Among these drugs, barbiturates were popular for some time. Their original purpose was to sedate heavily or induce sleep. There are many similarities among barbiturates and they can be used interchangeably, but they have been promoted as if they were thoroughly different. They were also originally thought of and often promoted as safe. Veronal, introduced by Bayer, exemplifies the pattern. It was the first barbiturate, marketed in 1903, and was advertised as "absolutely safe and without toxic effects". Within 10 years, reports of fatal overdose emerged.[6]

The recognition of dependence on the drugs came much later. This was partly due to the failure to define precisely the terms addiction, habituation, tolerance and dependence. There was much confusion among the four. Because barbiturates were prescribed for long periods in individual patients, withdrawal syndromes were rarely identified. When withdrawal did become evident upon discontinuation of the drugs, this was mistaken for a recurrence of the original condition and the patient would be put back on therapy.

By the 1950s, the evidence was incontrovertible that barbiturates were true drugs of addiction, but overprescribing continued. In the UK, barbiturate consumption more than doubled in the 1950s and continued to rise into the next decade. A 1962 editorial in *The Practitioner* suggested that too many doctors were taking the line of least resistance and "prescribing barbiturates as a blunderbuss remedy for all the anxieties and stresses" of life.[7]

Barbiturates are still on the market in most countries. Their only dubious distinction "is that of being the drugs of choice for suicide, for which they are extremely effective".[8] They should not be used to treat anxiety,[9] or as sedatives.[10] They have few indications today, other than as anticonvulsants to control epileptic seizures, as anaesthetics, and for a diminishing number of elderly people who have been using them for many years and for whom withdrawal would be dangerous.

Barbiturates have often been combined with other drugs such as analgesics, antispasmodics, antimigraine and anti-asthma products. There is no justification for these combinations.[10a]

Types of psychotropic drugs

Hypnotics

Benzodiazepines
- flunitrazepam
- loprazolam
- lormetazepam
- nitrazepam
- temazapam
- triazolam

Others
- chloral hydrate
- chlormethiazole
- chlormezanone
- dichloralphenazone
- methyprylone
- triclofos sodium
- zopiclone

Antihistamines
- promethazine

Barbiturates
- amylobarbitone
- butobarbitone
- cyclobarbitone
- heptabarbitone
- phenobarbitone
- quinalbarbitone

Anxiolytics/Tranquillisers

Benzodiazepines
- alprazolam
- bromazepam
- chlordiazepoxide
- clobazam
- clorazepate
- diazepam
- ketazolam
- lorazepam
- medazepam
- oxazepam
- prazepam

Others
- buspirone
- chlormezanone
- meprobamate

Antidepressants

Tricyclics/Cyclics
- amitriptyline
- butriptyline
- clomipramine
- desipramine
- dothiepin
- doxepin
- imipramine
- iprindole
- lofepramine
- maprotiline
- mianserin
- nortriptyline
- protriptyline
- trazodone
- trimipramine
- viloxazine

Monoamine oxidase inhibitors
- iproniazid
- isocarboxazid
- phenelzine
- tranylcypromine

Others
- flupenthixol
- fluvoxamine
- lithium
- tryptophan

Anti-psychotics

Phenothiazines
- chlorpromazine
- fluphenazine
- methotrimeprazine
- pericyazine
- perphenazine
- prochlorperazine
- promazine
- sulpiride
- thioridazine
- trifluoperazine

Butyrophenones
- benperidol
- droperidol
- haloperidol
- trifluperidol

Diphenybutylpiperidines
- fluspirilene
- pimozide

Thioxanthenes
- chlorprothixene
- flupenthixol
- zuclopenthixol

Others
- oxypertine

Taming people: the benzodiazepines

The benzodiazepines gradually superseded barbiturates as treatments for anxiety and sleep disorders during the 1950s and 1960s. Before they were introduced, the first alternatives to the barbiturates in the 1950s were products such as meprobamate, a barbiturate-like substance. Although drugs like this were claimed to be much safer, they too produced dependence. Meprobamate is less effective than benzodiazepines, has a higher risk of drug addiction, is more dangerous in overdose, produces more adverse effects, and has no advantage over the benzodiazepines.[11] Despite these problems, in 1984 doctors in the UK wrote 150,000 prescriptions for one brand of meprobamate (Equanil).[12] The *British National Formulary* considers it "less suitable for prescribing".[13]

The benzodiazepines – now among the most frequently prescribed drugs worldwide[14] – owe their existence to a chance discovery. A few hundred milligrams of a chemical substance lay forgotten in the corner of a Hoffman-La Roche laboratory after its first synthesis by chemist Dr Leo Sternbach in 1955. Other projects in the lab had taken priority and it was not until a clean up two years later that the substance was rediscovered and tested. The new chemical – called chlordiazepoxide – was found to tame aggressive animals without seeming to sedate them. The new drug was subsequently marketed as Librium, and the benzodiazepine era was born.[15]

Roche launched Librium in 1959. Almost inevitably, the first reports of dependence of the barbiturate type appeared in 1961.[16] By 1963, Roche had cornered the anti-anxiety market with the launch of a second benzodiazepine, diazepam (Valium), which became the most widely prescribed drug of this type. It also became the benchmark for the entire class of sedative chemicals. Safety, particularly in overdose, was a prime selling point. However, Valium, like Librium, was found to cause dependence. So too was Roche's third benzodiazepine, nitrazepam (Mogadon), launched in 1965 as a sleeping pill.

A clear pattern was emerging with these and the later benzodiazepines: the product, although similar to its earlier rivals, was launched with extensive promotion that focused on the safety of the drug compared to barbiturates, that failed to mention the possibility of dependence, and that tried to define a fragile difference on the basis of poorly controlled trials.

However, benzodiazepines are far from safe. Between 15 and 44% of long-term users become dependent on the drugs.[17] Overdose is also a problem. In 1988, nearly 1.4 million incidents of overdose were identified in the USA. Benzodiazepines accounted for the highest number of toxic exposures reported in patients older than 17 years of age, and they increased morbidity and mortality in incidents of mixed overdose.[18]

Common side effects of these drugs include: drowsiness, light-headedness, sedation, lack of coordination, difficulty in walking. More rare adverse effects include dizziness, headaches, stomach aches, skin rashes, blurred vision, changes of libido, slurred speech, blood disorders, and jaundice.[19] The elderly are more sensitive to these adverse effects, many of which can be mistaken as signs of senile dementia. The lack of coordination is a concern as it can lead to falls and hip fractures.[20] Diazepam, in particular, was found to have a high association with falls, leading researchers to suggest that it should not be used in the elderly.[21] (See the box on page 194 on psychotropic drugs and the elderly.)

Long-term use of benzodiazepines may cause psychological impairment and brain damage.[22] Even temporary use of a benzodiazepine could provoke long-term, sometimes permanent changes in the brain. Neuroscientist Prof. David Grahame-Smith says, "just as experience alters our future behaviour so do drugs".[23]

One researcher has stated that the effects of the shorter acting benzodiazepines such as alprazolam (Xanax by Upjohn) can induce "a fundamental change in the homeostasis [tendency towards chemical equilibrium] of the brain". It can take the brain from six to 18 months to recover after use of the drug has been stopped.[24]

Some commentators have even argued against the use of benzodiazepines in severe anxiety and sleep disturbance. They claim that benzodiazepines simply do not work and do more harm than good by creating anxiety and insomnia in the long run. Gavin Andrews, Professor of Psychiatry in Australia, says that "benzodiazepines do not cure any anxiety disorders – they suppress symptoms which may return when the drug is stopped".[25] That opinion is reinforced by Samuel Cohen, a British psychiatry professor, who says, "the time has come to state clearly that there is no use for these drugs in the treatment of anxiety."[26]

Overprescribing

At least 25 types of benzodiazepines have been marketed over the years.[27] There is little to choose among the benzodiazepines in terms of either safety or efficacy. "As far as any real distinctions between the differently labelled pills are concerned, they are as subtle as those between a brick and a half brick."[28]

With so many brands available, encouraging a "pill for every ill" mentality, doctors not only began to overprescribe but also to overdiagnose – to seek a match between complaints from a patient and the

descriptions of symptoms found on the advertisement for the latest benzodiazepine. As one commentator puts it, "whether or not our patients are hooked on the drugs, the doctors are certainly hooked on the diagnoses".[29] (See the box on page 188 about some of the many reasons that people have been prescribed benzodiazepines.)

In the right hands, at the right dosage, for the right length of time, benzodiazepines can be useful. They can give a person valuable breathing space and time when an emotional crisis becomes intolerable. However, the powerful chain of production, promotion and prescribing grossly distorts the appropriate use of these drugs.

In the UK, the Committee on Safety of Medicines (CSM) advises that benzodiazepines should only be used for the short-term relief (two to four weeks only) of anxiety or insomnia that is severe, disabling or subjects the individual to extreme or unacceptable distress. Their use for "mild" anxiety is inappropriate and unsuitable.[30]

Unfortunately, misuse through overprescribing is common. In the UK, there is "appalling clinical practice" by some prescribers who do not attempt to make a proper diagnosis before prescribing benzodiazepines.[31] During a three-month period, as many as 73% of general practitioners and 68% of consultants in one UK health authority were found to have prescribed a psychotropic drug to a child of 17 years or younger.[32] In South Africa, one report concluded:

> "it cannot be postulated that the majority of patients who were prescribed benzodiazepines for anxiolysis in this hospital were experiencing severe anxiety. The use of these compounds in this context is therefore unwarranted."[33]

In France, pharmacists believe that doctors give in too readily to patients' demands and overprescribe benzodiazepines for minor states of anxiety and "poorly defined morbid symptoms and states", thereby "taking refuge in the prescription".[34] In Barcelona, Spain, a 1990 study found widespread overuse of psychotropics, two-thirds of which were benzodiazepines.[35]

In Canada in the mid-1980s, about one in 10 people used a benzodiazepine at least once a year. Of these, again one in 10 continued their use for more than one year.[36] In the UK in 1985, more than 23% of the population took a tranquilliser at least once during the year. Of these, 35% (3.5 million people) took tranquillisers for periods of four months or more, the time after which the drugs no longer help, and far longer than they should normally be prescribed.[37] In 1987, there were about 25 million prescriptions for benzodiazepines issued in the UK – 15 million for use as hypnotics and 10 million to treat anxiety.[38]

Women and psychotropic drugs

Many studies show that women throughout Europe and North America are prescribed tranquillisers twice as often as men.[1] It is not uncommon for women who were prescribed a short course of tranquillisers for some reason to still be taking the drug some 10 or 20 years later.[2] More than two-thirds of prescriptions for antidepressants in the USA are for women.[3]

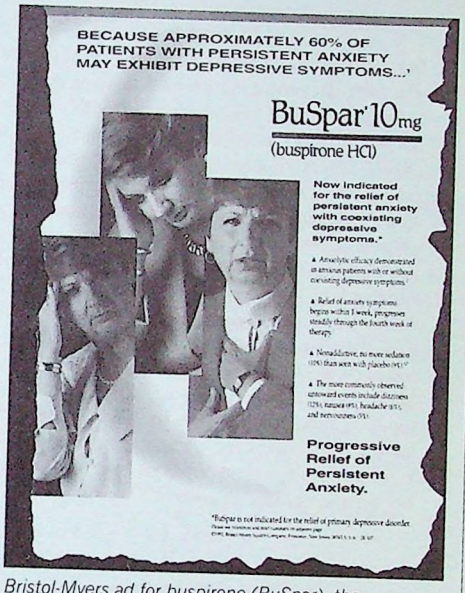
There are many opinions as to why women are prescribed more psychotropic drugs. Simplistic solutions to this question are suggested by some studies, which show that they are more likely to suffer from psychiatric problems than men[4] and by others, which suggest that women complain more than men.[5] However, both these explanations may hide more fundamental problems related to women's status in society. Women are more likely to be engaged in low-paid jobs outside the home, or be working in isolated situations at home. There may be a lack of external childcare facilities, unequal distribution of responsibilities for childcare within the family, and a breakdown of support from the traditional extended family. An increasing number of households in many countries are headed by a woman who has the sole responsibility for bringing up her children and for earning the principal income. A large proportion of these households face disadvantage and poverty – all contributory factors to anxiety, stress and depression.

Doctor's attitudes can contribute to women receiving more psychotropic drugs. Doctors will often perceive a woman's physical complaint as inherently psychological and thus give mood-changing drugs.[4] This is not helped by the images used in much of the promotional material for psychotropic drugs. Women are more often portrayed as suffering from diffuse emotional symptoms, while men are shown suffering from anxiety as a result of work or accompanying organic disease.[6] In the USA, Pfizer's promotional material to launch its new antidepressant, Zoloft (sertraline), features a woman in her thirties who is able to move "from depression... into the mainstream" as a result of the drug.[7]

Frequently the woman is targeted on behalf of her family: "Treat one... six people benefit", was how one advertisement expressed it, while showing a picture of a family with the focus on the mother.[8]

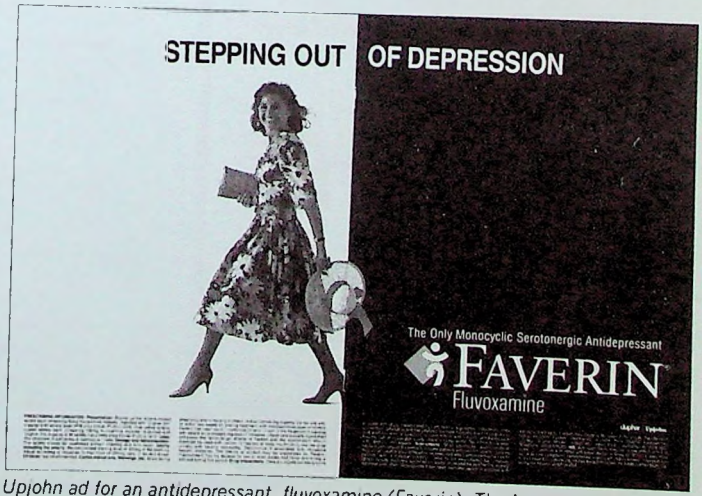
Many women find it difficult to get support in coming off the drugs. Self-help groups that have formed in many countries in recent years are one step in the right direction, helping women gradually to come off tranquillisers. More effective, however, would be efforts to prevent misprescribing and overprescribing to women, and to ensure that tranquillisers stop being used as a solution for social problems.

"Where do you start tackling depression first?" postcard sent by Searle to doctors in the Netherlands in 1992 advertising an antidepressant



Bristol-Myers ad for buspirone (BuSpar), the American Journal of Medicine, June 1992

Sandoz promotion for doctors in India in 1990 suggesting that women be prescribed an antipsychotic, thioridazine, instead of diazepam



Upjohn ad for an antidepressant, fluvoxamine (Faverin), The Lancet, 12 Dec 1992

Sources:
1. Balter, A., et al, "A cross national comparison of anti anxiety and sedative drug use", *Current Medical Research and Opinion*, Vol 8 (Suppl. 4), 1984, pp5-18
2. Phillips. A., Rakusen, J. (eds) and the Boston Women's Health Collective, *The New Our Bodies, Ourselves* (2nd UK edition), London, Penguin Books. 1989. p68
3. Breggin, P., *Toxic Psychiatry*, London, Fontana, 1993, p186
4. Ashton, H., "Psychotropic drug prescribing for women", *British Journal of Psychiatry*, Vol 158 (Suppl. 10), 1991, pp30-5
5. Unlenworth, E.H., et al, "Symptom checklist syndromes in the general population", *Archives of General Psychiatry*, Vol 40, 1983, pp1167-73
6. Prather, J.E. and Fidell, L.S., "Sex differences in the content and style of medical advertisements" in: Gabe, J. and Williams, P., *Tranquillisers – social, psychological and clinical perspectives*, London and New York, Tavistock, 1986, p90
7. Critser, G., "Dealing a new antidepressant", *Harper's Magazine*, May 1993, pp54-5
8. Prather, J.E. and Fidell, L.S., op cit

But it is not only the doctors and patients who are hooked. The chain of dependence leads to the drug companies as well. Many companies that market benzodiazepines rely heavily on the income from their products and invest proportionately in marketing and sales representatives to ensure a steady flow of income.[39] When concerns were raised about the safety of Upjohn's triazolam product, Halcion, (see box on page 189 for details), the drop in sales contributed to a 2% decrease in the company's total operating profit during the first nine months of 1992.[40]

Swans and teddy bears: the new generation

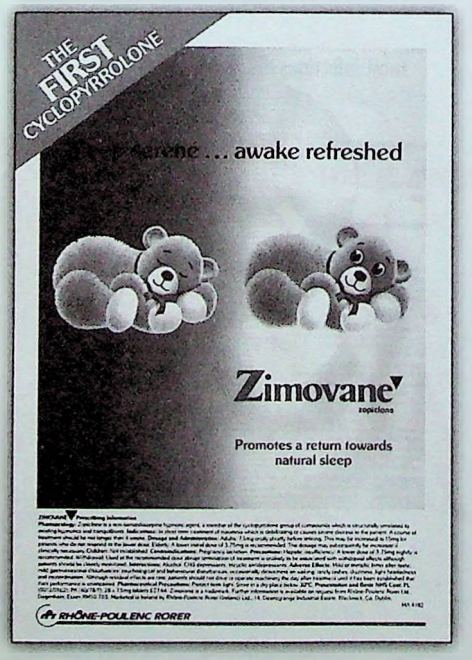
The pharmaceutical industry is following up the commercial success of benzodiazepines with a new wave of products. One of these, buspirone (BuSpar by Bristol-Myers), is described as being "as easy to stop taking as it is to start".[41] This idealised picture has led to promotion depicting an air traffic controller who needed "anxiolytic therapy, but alertness is part of his job" or, the image of a swan swimming serenely on calm waters: "Anxiety therapy pure and simple". Advertisements claimed there was no evidence of dependence or abuse potential. But it may simply be too early to know. "We need much more information about its benefits and risks over time", is the way one guide to drug use expresses it.[42] In the USA, product information makes it clear that "the efficacy of buspirone for more than three or four weeks has not been demonstrated in controlled trials".[43]

Why people have been prescribed tranquillisers

bereavement
emotional upsets
nursing a sick wife
husband's accident
socialising
after the flu
dry eyes
hysterectomy
alcohol problem
alcoholic father
sexual abuse
stomach trouble
business problems
coping with:
  active/crying baby
  handicapped child
  demanding mother
shift work
bankruptcy
fear of dying
lack of confidence
homelessness
mother committed suicide
jury service
work pressure
loss of hearing
interview nerves
dizziness
stroke
shyness
childhood insecurity
isolation
family problems
broken neck
change of job
violent husband
prison
infertility
cystitis
cooker blew up
claustrophobia
illness
postnatal depression
exam nerves
fatal illness
disc trouble
divorce
menopause
bad fall
rugby injury
rape
car crash
headaches
back pain
mastectomy
thyroid
driving test
cat died
redundancy
hay fever
vertigo
palpitations
moving home
asthma
retirement
abortion

Note: These reasons were given in inquiries to a UK organisation (TRANX), which provided help to people addicted to tranquillisers.

Source: Jerome, J. and Bilgorri, L., *The Lost Years: tranquillisers and after – the effect minor tranquillisers can have on our life and our families*, London, Virgin Books, 1991, p24



Rhone-Poulenc advertisement for zopiclone (Zimovane), The Lancet, 17 Aug 1991

Halcion: a scandal?

By the end of the 1970s, concern had grown about the hangover effects of the longer acting benzodiazepines. Upjohn introduced a short acting hypnotic, triazolam, sold as Halcion or Somese. The promotional material said that "when short-term problems cause insomnia, triazolam lets patients sleep on them".

While the drug did not accumulate in the body, reports of side effects quickly accumulated. An early Dutch report said triazolam could cause acute psychosis, paranoia and confusion. The Dutch government subsequently banned the drug in mid-1979. It was allowed back on the market in the Netherlands in a reduced dosage form in 1990.

In other countries, the controversy waxed and waned. Reports of memory loss, confusion, bizarre and abnormal behaviour surfaced all over the world. Professor Ian Oswald, a specialist in sleep disorders, said in 1982 that the combination of short half-life and long interval between doses led to daytime anxiety.[1] Tolerance to the drug's hypnotic effects was also identified as a problem, as was rebound anxiety when the drug was stopped. Seven years later, Oswald said that Upjohn had not properly investigated these effects with long-term trials. He claimed that triazolam "should never be sold".[2] Other critics agreed, arguing that the drug was not an efficient hypnotic in the first place, and the evidence of adverse effects only reinforced its undesirable nature. "The social consequences and even criminal potential of triazolam are frightening."[3]

It was the possible link between the drug and criminal behaviour that led to widespread publicity of some of these concerns in 1991. Mrs Ilo Grundberg, accused of murder in the USA, was acquitted after claiming that the use of Halcion had caused her to become violent and kill her mother in 1988. She went on to sue Upjohn for damages and the case was settled out of court in 1991. Some of the evidence that emerged indicated that errors had been made in reporting the information from one of the early clinical trials of the drug, errors that downplayed the possibility of serious psychological side effects. After reviewing this information, the UK Committee on Safety of Medicines (CSM) asked Upjohn to withdraw the drug. When the company refused, the CSM withdrew the drug's licence. This triggered off a wave of withdrawals in at least 13 other countries.[4] In April 1993, the Medicines Commission in the UK, an advisory body to the Ministry of Health, recommended re-instating Halcion.[5] However, the UK government decided to keep the drug off the British market because of concerns about its safety.[6]

In several other countries, the drug has been allowed to remain on the market, but at reduced dosage levels. However, there is little evidence to support claims that triazolam has distinct advantages over other drugs in its class. An editorial in the *British Medical Journal* makes the point that memory impairment, psychiatric disturbance and rebound insomnia are "more common" with triazolam than with other benzodiazepines. The editorial concludes: "triazolam has no compelling singular benefits that outbalance its risks".[7]

Graham Dukes, professor of Drug Policy Studies at Groningen University, calls the Halcion affair "one of the drug scandals of the century, one of those which is only just coming out into the open far too late. It's a scandal because it undermines the entire system on which the safety of patients with drugs is based, the system of trust."[8]

References:
1. Morgan, K. and Oswald, I., "Anxiety caused by a short-life hypnotic", *British Medical Journal*, 27 Mar 1982, p942
2. Oswald, I., "Triazolam syndrome 10 years on", *Lancet*, 19 Aug 1989, pp451-2
3. van der Kroef, C., "Triazolam", *Lancet*, Vol 338, 6 Jul 1991, p56
4. Anon., "Upjohn's CNS sales down", *Scrip*, No 1776, 4 Dec 1992, p11
5. Dyer, C., "Experts urge sleeping pill ban be lifted", *Guardian*, 15 Apr 1993
6. Brahams, D., "Triazolam licensing in UK", *Lancet*, Vol 341, 19 Jun 1993, p1587
7. McGuggin, P. and O'Donovan, M., "Editorial", *British Medical Journal*, 10 Apr 1993
8. Dukes, M.N.G., interviewed on BBC's *Panorama* programme on Halcion, 14 Oct 1991

Most textbooks have also ignored a potentially hazardous problem with buspirone. Unlike minor tranquillisers, it affects the dopamine receptors, blocking their activity. Suppression of dopamine activity by neuroleptics or major tranquillisers such as chlorpromazine (Largactil) is known to cause tardive dyskinesia (repetitive movements of the hands, wrists, lips, tongue and jaw). While buspirone's mode of action differs from the neuroleptics, "the impact is sufficiently similar to raise red flags".[44]

Other new drugs such as zopiclone (Zimovane by Rhone-Poulenc) are promoted as safer than the benzodiazepines. "Sleep serene... awake refreshed" proclaims an advertisement depicting a cuddly teddy

bear. On the basis of several clinical trials, the advertisement said that there was "no evidence of dependence in clinical use". However, a *Lancet* editorial in 1990 attacked the promotion, arguing that the claims made about dependence were "inaccurate to the point of being irresponsible".[45] Only a year after the drug was launched in the UK, the CSM issued a report that, based upon adverse drug reactions received, drew attention to the risk of dependency on long-term use of zopiclone.[46] The irresponsible inaccuracy continues: in October 1992, in Malaysia, a Rhone-Poulenc advertisement for Imovane (its name for zopiclone in Asia) in the leading prescribing guide, *DIMS*, told doctors that "No serious adverse reactions have been seen".[47]

In developing countries

As that example shows, if there are problems with psychotropic drugs in industrialised countries, the situation in developing countries is typically much worse. According to the World Health Organization (WHO), the rational use of benzodiazepines and other psychotropic drugs is made more difficult by:

- overuse of psychotropics to control troublesome patients when staffing levels at care facilities are inadequate;
- use of inappropriate psychotropics due to difficulties in diagnosis with the limited facilities available;
- sales in the marketplace of substances from illicit sources; and
- inappropriately low dosage or short duration of administration due to financial constraints.[48]

A further complication is the general availability of psychotropic drugs without a prescription.

Another problem is the poor quality of information about these drugs. In late 1988, promotional claims for benzodiazepines in Pakistan were described by one British doctor as "misleading.... If these claims are correct, then British doctors and their patients are missing out on a therapeutic revolution."[49] Sandoz said that patients who take its brand of temazepam (Restoril) "do not experience drug dependence", while Parke-Davis both blamed the patient for the problem of drug dependence and reassured the doctor that it was not likely to happen with its prazepam (Verstan) because the drug "may provide an advantage in certain patients prone by history to drug misuse".

Also in late 1988, Roche encouraged doctors in Malaysia to relax about the simplicity and safety of its midazolam (Dormicum) by describing the drug as the "sleep starter: Switch light off... switch sleep on".

In Peru in 1991, Multifarma was promoting its alprazolam (Alpaz) as a treatment for virtually every condition of daily life. It promised relief for:

- the "syndrome of the modern woman" – who suffers from increased worries about work, and an increased workload, emotional worries and stress;
- the "syndrome of today's man" – who worries about the future, his increased responsibilities, frustrations at not reaching his goals, financial problems and stress;
- the "syndrome of the housewife" – who worries about the children's education, having too much work, financial problems, fear of domestic accidents and a fear of the house being burgled; and
- the "syndrome of the elderly" – who fear being lonely, worry about their health and future, have limited finances, and lack affection.

With sales promotion like this, it is little wonder that the market for hypnotics and tranquillisers in Peru has reached US $5.4 million.[50]

Roche promotes routine use of midazolam (Dormicum) as a sleeping pill, Malaysia, DIMS, Oct 1988

Medicalisation of life

This "medicalisation of life" helps to sell more drugs. One report talks of the industry's "encouragement of symptomatic prescribing".[51] However it is described, this overuse of drugs also provides a convenient solution for many health workers who simply have too little time to devote to their patients. It may be that what many people need is sympathy and someone to

talk to. Where that need is not met because of isolation, poverty, or other causes, the doctor or health worker is looked upon as someone who can help untangle a complex collection of problems. However, the doctor or health worker is often powerless to change anything. With limited time and an ever-increasing array of powerful drugs promising miraculous results, is it any wonder that there is a growing market for these products?

The forerunners of modern psychotropic drugs were often described as chemical straightjackets, providing the means to restrain difficult patients with methods that seemed, on the surface, more humane. There is a lingering concern that today's chemicals could still be used as control mechanisms, or be used to replace the social contact and personal care that is often needed to deal with psychological problems. The high use of psychotropic drugs among the elderly and among women is a worrying indicator (see the boxes on pages 194 and 186). Drugs can simply serve to further disempower people who may already be feeling the impact of some form of disadvantage in society.

As one leading psychiatrist puts it: "It is understandable that some people want to try to handle their problems through psychiatric or recreational drugs, but should doctors endorse this dangerous and self-defeating avenue as a form of medical treatment? As physicians and psychotherapists we should empower our patients to trust themselves and their capacity to triumph over frightening emotions. We should help them overcome anxiety through self-understanding, improved self-control of their minds and actions, more courageous attitudes and more successful principles of living."[52]

Consultant psychiatrist, Brian Ballinger, says: "More emphasis should now be placed on managing sleep disorders and anxiety without using drugs."[53]

Controlling benzodiazepines

Several countries have taken initiatives to tighten the control of benzodiazepines. For a long time, the Norwegian government has exemplified WHO's concept of focusing on essential drugs by limiting the numbers of products licensed. For a product to receive a licence, it has to be more effective than those already on the market and meet a clear medical need.[54] Even so, one commentator felt that the 10 benzodiazepines and nine antidepressants on the market could be effectively halved without causing any limitations on therapy.[55]

In April 1985, the UK government introduced a limited list of drugs that could be prescribed under the National Health Service in seven major therapeutic areas, including benzodiazepines as hypnotics. It was an effort to save money, but also to introduce more rational prescribing.[56] The original plan was to have doctors restrict benzodiazepine use to just three of the 17 products then on the market in the UK. However, following strong lobbying from the pharmaceutical industry, the list was expanded to include another six benzodiazepines.[57]

This concept of a limited list is one that is also frequently used at hospital or clinic level. Many hospitals in different countries have their own versions of limited lists – drug formularies – which enable them to select the safest, most effective and, usually, least expensive drugs.[58]

A UK hospital designed a policy to ensure that no new addicts are created while they were in hospital and that people who were already addicted were weaned off the drugs as safely and rapidly as possible. Benzodiazepines were only used where strictly necessary, and not at all for the elderly. Hypnotics were not given for more than five days. No one was discharged with a supply to last more than three days. Alternatives to benzodiazepines were actively encouraged.[59]

In the USA, some states have attempted to restrict benzodiazepine use by law. A controversial approach by New York State effectively placed benzodiazepines under the same regulatory control as opiates, barbiturates and amphetamines. Among its aims, the policy hoped to reduce inappropriate prescribing. During the first year of operation, there was a 27-53% decrease in benzodiazepine prescriptions.[60] However, critics of the scheme point to increases in the use of other psychotropic drugs.[61] The debate on the effectiveness of the New York scheme continues. At any rate it serves as a reminder that no strategy can be used that is haphazard in rationale, motive and execution. Simply wiping away part of the problem without providing workable alternatives – non-drug therapy for anxiety, better long-term community care policies – will not bring real change.

Antidepressants

Many forms of depression lie on a continuum that spans from "feeling blue" to being unable to cope with life and feeling suicidal. All too often, the whole range of conditions are treated with drugs, whether or not such treatment is rational.

Identifying those forms of depression that could benefit from drug therapy is not always easy. Social, economic and physical factors can all play a role in depression. Antidepressant therapy should be considered only after the nature of the symptoms and causes of depression has been determined.[62] "Some patients may need individual or group psychotherapy, others may respond to counselling or to drugs, some just want a new house and a cheque for £50,000, others want a new husband or wife, all need to be taught how to relax."[63] As well, 30% of

people may respond to placebo[64] and spontaneous improvement in depression occurs in at least one quarter of people within the first month or so, and in one half or more over a few months.[65]

Nonetheless, antidepressants are popular drugs. In the USA, they are the second most commonly prescribed drugs after tranquillisers, with at least 34 million prescriptions a year being written.[66]

There are three main types of antidepressants: tricyclics and other cyclics, which are the most commonly used; monoamine oxidase inhibitors (MAOIs); and the newer, second generation drugs such as trazodone, fluvoxamine, fluoxetine and sertraline.

Many antidepressants have been on the market for three decades. These include the tricyclics imipramine (Tofranil) and amitriptyline (Domical, Elavil) and the MAOI, tranylcypromine (Parnate). They took over from stimulants such as the amphetamines in the late 1950s. Despite manipulation of the basic tricyclic nucleus which has resulted in many different drugs, the overall range of antidepressant efficacy has not changed.[67] Or, as one doctor put it, "since 1958, when imipramine (Tofranil) was first reported to be effective in depression, no other antidepressant has been widely shown to be any more effective".[68]

The pharmaceutical industry argues that the wide choice of different but broadly similar drugs is so that the physician can select the most appropriate drug on the basis of individual response. One method of selection is on the basis of side effects. However, there is little to choose among the various drugs. All tricyclics produce anticholinergic effects: dry mouth, blurred vision, constipation, difficulty in passing urine. The other side effects include sedation, precipitation of epilepsy, tremor, nausea, hypomania and confusion. Cardiovascular effects, including low blood pressure, have also been reported.[69]

One psychiatrist goes further: "evidence for their [tricyclics'] usefulness is very slim indeed.... They have a dulling effect on the mind... have a sedative effect... can cause withdrawal effects... are lethal in overdose.... They are in many ways neuroleptics in disguise.... When the individual tries to stop taking them the cholinergic system rebounds with great force, making it hard to get off them."[70] This dependency syndrome in itself is sufficient reason for caution in the use of antidepressants.

MAOIs can also produce severe side effects. "The potential toxic effects of the MAO inhibitors are more varied and potentially more serious than are those of most other groups of therapeutic agents used in the treatment of psychiatric patients."[71] They interact dangerously with many foods and with other drugs, causing a dramatic rise in blood pressure.[72] A special diet has to be followed. Less serious side effects include: dizziness, headache, inhibition of ejaculation and urination, constipation, fatigue, dry mouth, blurred vision, and skin rashes.[73] Withdrawal of the drug – as with other antidepressants – must be gradual. Sudden withdrawal can cause a range of symptoms including nausea, vomiting, loss of appetite, headache, insomnia, and anxiety.[74] Insomnia and anxiety may even occur when the drug is withdrawn gradually.[75]

Although there is general acceptance that MAOIs "do not seem to be the best agents for most psychotic depressions", they still find limited use in certain patients with "atypical" symptoms.[76] However, the difficulties with both the MAOIs and the first tricyclics have led to research into new drugs.

The new generation: a breakthrough or a breakdown?

In January 1988, Eli Lilly launched one of these new drugs, fluoxetine (Prozac). *Newsweek* magazine subsequently devoted a cover story to what it called a "breakthrough drug for depression". Even some doctors took it simply because it made them feel better.[77]

By 1990, Prozac had global sales of $600 million,[78] rising to more than $1 billion by 1992, moving it into the top 15 drugs according to sales.[79] An estimated four million people have been treated with Prozac worldwide.[80] This massive use of the drug was not in accordance with expert opinion about the drug: "the newer agents are not more effective than the standard tricyclic drugs".[81]

Much of the excitement surrounding Prozac was because the drug worked in a different way from the first generation products. It was thought that because it affected the neurotransmitter serotonin, this would make its impact more selective. There is a danger in taking this view: "There should be no comfort associated with the idea that Prozac is selective for serotonin. The brain, an integrated organ blessed with harmonies and balances beyond our ken, is thrown out of balance by any such biochemical intrusion."[82]

Though promoted as a safer alternative, fluoxetine can cause severe side effects such as uncontrollable movement, inappropriate secretion of antidiuretic hormone, serum sickness, sexual dysfunction, stuttering, tics, hearing loss, manic episodes, paranoid reactions, and intense suicidal feelings. It also interacts dangerously with other psychotropic drugs.[83]

Reports of increased suicidal tendencies have focused attention on fluoxetine.[84] Though it can be argued, and has been by Eli Lilly, that it is depression itself that causes suicidal tendencies, not one of these patients felt suicidal before taking the drug. More

than 70 lawsuits have been filed in the USA against Lilly, although none have come to trial. Lilly has also provided evidence for the prosecution in cases where criminal defendants are claiming that the use of Prozac led them to engage in violent behaviour. This line of defence has been rejected in all 10 cases tried.[85]

In September 1991, a meeting of the US FDA's Psychopharmacologic Drugs Advisory Committee found no "credible evidence" to support a conclusion that the use of antidepressant drugs in general and Prozac in particular causes the emergence or intensification of suicidal acts or other violent behaviours.[86] There were, however, some "reservations" among members of the committee, some of whom suggested that "further study might be needed to identify potential high risk patients".[87]

While many patients have been taking the drug for a long time, the effectiveness of fluoxetine has not been tested in controlled trials of more than four to five weeks. Its long-term usefulness and effects of possible withdrawal have not been sufficiently analysed.[88] Another concern is that its adverse drug reaction profile is similar to other drugs that have been withdrawn for safety reasons, such as Astra's zimeldine (Zelmid), Hoechst's nomifensine (Merital), and tryptophan. Overuse of fluoxetine as a result of misleading promotional material could cause a "surfeit of serious ADRs".[89]

Table 10A-2
Adverse effects of some newer antidepressants

Drug	Comment
viloxazine	antidepressant effects differ little from those of standard drugs; nausea which appears dose related limits usefulness
maprotiline	rashes and convulsions are among the adverse effects; careful supervision is required
mianserin	blood disorders such as aplastic anaemia and agranulocytosis have been reported; liver disorders have also occurred; careful supervision is required
trazodone	priapism (persistent erection of the penis) has been reported
fluvoxamine	nausea and vomiting are common effects, convulsion has been reported
fluoxetine	nausea and more severe adverse effects have been reported; too new to evaluate
sertraline	too new to evaluate

Sources: Feely, J. (ed.), *New Drugs*, London, British Medical Journal, 1991, pp303-5; BMA and the Royal Pharmaceutical Society of Great Britain, *British National Formulary*, London, BMA and The Pharmaceutical Press, No 23, Mar 1992, pp151-2

The role of the newer generation of antidepressants is as a second line alternative when the older drugs do not work for patients with severe depression. "Therefore it is difficult to put the widespread use of fluoxetine into perspective.... The still evolving data on the recently introduced antidepressant drugs remind us that only a few are truly novel."[90] Generally, "in no case has the efficacy of the new antidepressants been shown to exceed that of the tricyclics".[91] As well, information about adverse effects is still evolving. Table 10A-2 summarises this information for some of the newer antidepressants.

But there are alternatives to drugs:

> "The vast majority of people overcome depression without resort to any mental health services. They do so by virtue of their own inner strength, through reading and contemplation, friendship and love, work and play, religion, art, travel, beloved pets, and the passage of time – all of the infinite ways that people have to refresh their spirits and to transcend their losses."[92]

Antipsychotics

Many millions of people are treated both inside and outside mental institutions with antipsychotics (major tranquillisers or neuroleptics) for conditions such as schizophrenia and other severe psychiatric disorders. These drugs have serious risks of major side effects – including tardive dyskinesias that may not be reversible.[93] They are not "in any sense a cure" for the conditions for which they are used; rather they are best seen as drugs that "can shorten the duration of an acute psychotic episode and increase the time interval between relapses".[94]

One leading pharmacology textbook points out that knowledge about the use of drugs in mental and behavioural disorders "is in its infancy. In relation to drug therapy, virtually nothing is known about the causes of mental disease or about how many drugs may work to relieve symptoms, though many pharmacological *facts* are known.... In addition, there is a dearth of well-designed therapeutic trials such as are essential to determine what drugs can do."[95]

Another important point is that the use of these drugs alone "does not constitute optimal care of psychotic patients. The acute care, protection, and support of acutely psychotic patients, as well as mastery of techniques employed in their long-term care and rehabilitation, are important medical skills."[96]

Although these drugs should be used with caution, usage patterns among some population groups such as the elderly suggest that these powerful drugs are

Psychotropics and the elderly

The aging process affects the ability of the body to use drugs. Differences in the absorption, distribution and clearance of a drug, make an elderly person more sensitive to both its desired and undesired effects. Often a drug will affect an elderly person in a strikingly different way from that expected in someone younger.[1]

Studies in the USA show that the elderly, who make up one-sixth of the total population, are prescribed one-third of all tranquillisers and more than half of all sleeping medications.[2] Studies from other countries confirm that the elderly receive a disproportionately high amount of prescriptions for benzodiazepines.[3] In Australia, for example, hypnotics were prescribed in "alarming quantities", particularly for the elderly. "Sleeping and ageing have proven to be bonanzas to the marketer.... Notwithstanding the plain fact that older people require and get less sleep, a sleep market is created with programming directed to the elderly. Salvation is offered for the sleepless: a 'quiet, restful, splendid sleep'. All that is required is a simple pill."[4]

Hypnotics or tranquillisers in "average" doses may cause confusion and unsteadiness in an elderly person. A benzodiazepine sleeping pill which would be largely excreted by most younger people within eight hours may "hang over" throughout the whole of the next day.[5] With repeated use, concentrations of the drug can build up until toxic levels are reached.

This hangover effect was particularly noticed in the 1970s and 1980s when it was discovered that benzodiazepines with a long half-life (those that take a long time to be excreted) such as nitrazepam (Mogadon) were associated with confusion, disorientation and lack of coordination. All of these symptoms can be misdiagnosed as progressive brain disease or signs of dementia.

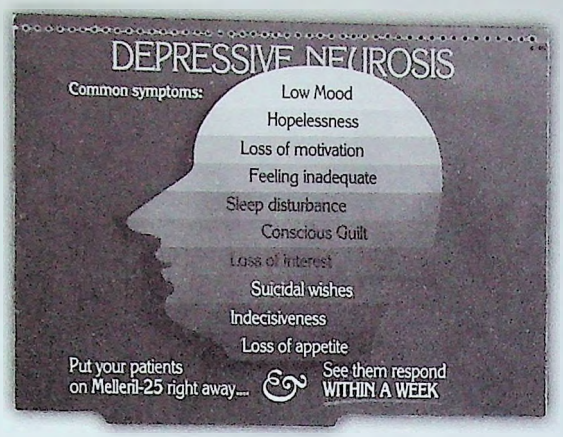
Long-term use of benzodiazepines has been associated with falls, hip fractures, daytime sedation and cognitive dysfunction in the elderly. However, "physicians are prescribing the greatest quantities of medications to those patients who can least well tolerate long-term hypnotic use."[6]

In residential nursing homes, the situation is often alarming. "Despite growing consensus about the serious adverse effects of psychotropic drug use in the elderly population, studies repeatedly show that one-fourth to one-half of all nursing home residents [in the USA] receive a major or minor tranquilliser." Frequently the greatest use takes place in those facilities where there is neither sufficient care nor adequate training of staff to look after people properly. "Low resource facilities are less likely to have well-planned social and recreational facilities. This can contribute further to chronic loneliness and disruptiveness and, ultimately, the chronic use of tranquillisers as a substitute for meaningful activity and social interaction. In effect, tranquillisers serve as a 'chemical restraint' or 'substitute' for safer, more effective, and more humane ways of care."[7]

Depression affects 10% of those over the age of 65.[8] However, antidepressant drugs may not be an appropriate response. The tricyclic antidepressants are associated with cardiovascular and anticholinergic effects such as dry mouth and blurred vision. This makes them "unattractive for the elderly".[9] The dangerous food and drug interactions that can occur with monoamine oxidase inhibitors (MAOIs), already make them second-line drugs for depression.[10] They may be particularly unsuitable for the elderly.

The search for more effective and safer antidepressants in the elderly has resulted in some acceptance of the newer generation of anti-serotonin agents as the solution. The role of drugs such as fluoxetine (Prozac) and sertraline remains to be established.

References:
1. Greenblatt, D.J., Harmatz, J.S., et al, "Clinical pharmacokinetics of anxiolytics and hypnotics in the elderly", *Clinical Pharmacokinetics*, Vol 21, No 3, 1991, pp165-77
2. Wolfe, S.M., Fugate, L., et al, *Worst Pills Best Pills*, Washington, Public Citizen Health Research Group, 1988, pp145-155
3. Collier, J., *The Health Conspiracy*, London, Century Hutchinson, 1989, p15
4. Jackson, D.M. and Soothill, R., *Is the Medicine Making You Ill?*, North Ryde, Australia, Angus & Robertson, 1989, pp28-9
5. Parish, P., *Medicines: a guide for everybody*, London, Penguin (6th edn. revised), 1989, p32
6. Schorr, R.I., Bauwens, S.F. et al, "Failure to limit quantities of benzodiazepine hypnotic drugs for outpatients: placing the elderly at risk", *American Journal of Medicine*, Vol 89, Dec 1990, pp725-31
7. Svarstad, B.L. and Mount, J.K., "Nursing home resources and tranquilliser use among the institutionalised elderly", *Journal of the American Geriatric Society*, Vol 39, 1991, pp869-75
8. Cohn, C.K, et al, "Comparison of sertraline and amitriptyline in elderly depressed patients", *Journal of Clinical Psychiatry*, Vol 51, No 12 (Suppl 12), Dec 1990, p28
9. Maletta, M.D., Mattox, K.M., et al, "Guidelines for prescribing psychoactive drugs for the elderly: part 1", *Geriatrics*, Vol 46, No 9, Sep 1991, p.44
10. BMA and the Royal Pharmaceutical Society of Great Britain, *British National Formulary*, London, BMA and The Pharmaceutical Press, No 23, Mar 1992, p156



Sandoz advertises an antipsychotic (thioridazine) to doctors in India in 1990 for treatment of symptoms such as "feeling inadequate" and "indecisiveness"

much overused. Schizophrenia is the most common reason for prescribing antipsychotics. However, schizophrenia and other psychoses are much less common among elderly people. Nonetheless, in the USA, for example, an estimated 750,000 people over 65 (not counting those in mental hospitals) are regularly using antipsychotic drugs, even though the total number of people over 65 estimated to have schizophrenia is less than one-eighth (92,000) of that number. Well over 80% of the elderly people in the USA who are taking antipsychotic drugs are using them needlessly.[97]

Ending the cycle of dependence

The history of the use of psychotropic drugs shows the need for regulatory control at several different stages. At the clinical level, adequately designed trials of new drugs are needed, particularly among populations who are most at risk from these drugs – the elderly and women. Approval procedures could consider the need for drugs. Better monitoring of and more effective responses to adverse effects would help. So too would more cautious prescribing to avoid the use of drugs as a palliative when social action is required. Tough measures to ensure high quality information and strict penalties for poor quality promotional material would also be a start.

Recommendations for action

1. Combination products containing a barbiturate should be banned. Single ingredient barbiturates should be removed from the general market and their use reserved for anaesthesia, some anticonvulsant therapy, and for limited use among named elderly patients who have been on them for some time.

2. Benzodiazepine tranquillisers should be prescribed only for the relief of severe symptoms of anxiety, or for severe sleep disorders, and then only for the shortest possible time and in the lowest possible dosages. Their use should be limited in the elderly.

3. Governments should strengthen controls to ensure that benzodiazepine tranquillisers are not illegally sold over the counter. Special attention should be paid to the promotion of benzodiazepines to ensure that their overuse is not encouraged.

4. National and local formularies and therapeutic guidelines should be developed for the treatment of anxiety, insomnia and depression. Where possible, non-drug solutions should be encouraged.

5. Governments and health worker associations should ensure that independent information is available for patients and prescribers about the rational use of psychotropic drugs, including adequate warnings about the risk of dependency on these drugs.

References:

1. Chaudhary, V., "Experts urge sleeping pill ban be lifted", *Guardian* (London), 15 Apr 1993, p2
2. Fitzsimons, C., "Addicts to sue over 'happy pill' misery", *Observer* (London), 14 Feb 1988
3. FIND/SVP, *The Market for Psychotropic Drugs*, New York, FIND/SVP, 1992, cited in: Anon., "Psychotropic sales $7.6 bill by 1996?", *Scrip*, No 1720, 22 May 1992, p26
4. Management and Marketing Corporation, *US Psychotherapeutic Agents Rx Strategies: Trends, Strategies, Threats and Opportunities*, Stamford, CT., Management and Marketing Corporation, 1992
5. Medawar, C., *Power and Dependence*, London, Social Audit, 1992, pp8-25
6. Ibid, p58
7. Ibid, p69
8. Lacey, R., *The Complete Guide to Psychiatric Drugs*, London, Ebury, 1991, p37
9. Parish, P., *Medicines: a guide for everybody*, London, Penguin (6th edn, revised), 1989, p68
10. Feely, J. (ed.), *New Drugs*, London, British Medical Journal, 1991, pp297-8
10a. Hartog, R. *Barbiturate Combinations: Risks without Benefits*, Bielefeld, BUKO Pharma-Kampagne and Health Action International, 1993
11. Parish, op cit, p68
12. Medawar, op cit, p73
13. BMA and the Royal Pharmaceutical Society of Great Britain, *British National Formulary*, London, BMA and The Pharmaceutical Press, No 23, Mar 1992, p139
14. Gaudreault, P., Guay, J., et al, "Benzodiazepine poisoning: Clinical and pharmacological considerations and treatment", *Drug Safety*, Vol 6, No 4, 1991, pp247-65
15. Winger, G., *Tranquillizers: The Cost of Calmness*, London, Burke, 1988, p27
16. Hollister, L.E., Mortzenbecker, F.P., et al, "Withdrawal reactions from chlordiazepoxide (Librium), *Psychopharmacologia*, Vol 2, 1961, pp63-8
17. Blenkinsopp, A. and Panton, R., *Health Promotion for Pharmacists*, Oxford, Oxford University Press, 1991, p183
18. Votey, S.R., Bosse, G.M., et al, "Flumazenil: a new benzodiazepine antagonist", *Annals of Emergency Medicine*, Vol 20, Feb 1991, pp181-8
19. Parish, op cit, p65
20. Wolfe, S.M., Fugate, L., et al, *Worst Pills Best Pills*, Washington, Public Citizen Health Research Group, 1988, p149
21. Cumming, R.G., Miller, J.P., et al, "Medications and multiple falls in elderly people: the St Louis OASIS Study", *Age and Ageing*, Vol 20, 1991, pp455-61
22. Jerram, T.C., "Hypnotics and sedatives", in: Dukes, M.N.G. and Beeley, L., (eds), *Side Effects of Drugs Annual 14*, Amsterdam, Elsevier, 1990, p35-44
23. Quoted in Medawar, op cit, p201
24. Steinberg, J., quoted in Breggin, P. *Toxic Psychiatry*, London, Fontana, 1993, p305
25. Andrews, G., "The management of anxiety", *Australian Prescriber*, Vol 14, No 1, 1991, pp17-19
26. Cohen, S.I., "Are benzodiazepines useful in anxiety?", *Lancet*, 7 Nov 1978, p1080
27. Winger, op cit, p27
28. Lacey, op cit, p22
29. Medawar, op cit, p113
30. BMA and the Royal Pharmaceutical Society of Great Britain, op cit, p133
31. Anon, "Media attention for council statement on BZDs", *Pharmaceutical Journal*, Vol 243, 1989, p209
32. Anon., "Psychotropic drug prescribing in children", *Scrip*, No 1590, 13 Feb 1991, p23
33. Summers, R.S., Schulte, A., Summers, B., "Benzodiazepine use in a small community hospital", *South African Medical Journal*, Vol 78, 15 Dec 1990, p724
34. Anon., "French benzodiazepine report calls for change", *Scrip*, No 1587, 1 Feb 1991, p4
35. Anon., "Psychotropic misprescribing in Spain", *Scrip*, No 1618, 22 May 1991, p9
36. Gaudreault, et al, op cit
37. Lacey, op cit, p19
38. Ashton, H., "Psychotropic drug prescribing for women", *British Journal of Psychiatry*, Vol 158 (Suppl. 10), 1991, pp30-5
39. Medawar, op cit, p112
40. Anon., "Upjohn's CNS sales down", *Scrip*, No 1776, 4 Dec 1992, p11
41. Anon., "Buspirone and gepirone – an expanding role in psychiatry?", *Scrip*, No 1482, 24 Jan 1990, p24
42. Parish, op cit, p64
43. *Physicians' Desk Reference*, Oradell, NJ, Medical Economics Company, 44th edn, 1990, p1308
44. Breggin, op cit, p311
45. Anon., "Zopiclone: another carriage on the tranquilliser train", *Lancet*, Vol 335, 3 Mar 1990, pp507-8
46. Anon., "Zopiclone (Zimovane) and neuro-psychiatric reactions", *Current Problems*, No 30, Dec 1990, p2
47. Anon., "No serious adverse reactions?", *Utusan Konsumer*, Jan 1993, p15
48. Ghodse, H., and Khan, I. (eds), *Psychoactive Drugs: Improving Prescribing Practices*, Geneva, WHO, 1988, p15
49. Birley, J.L.T., "Drug advertisements in developing countries", *Lancet*, 28 Jan 1989, p220
50. López Linares, R. and Phang Romero, C., *¿Promoviendo la Salud o los Negocios?*, Chimbote, Acción para la Salud, 1992, p11
51. Anon., *Scrip*, No 1587, op cit, p4
52. Breggin, op cit, p330
53. Feely, op cit, p300
54. Joldal, B. "Selecting drugs on the basis of need", *World Health Forum*, Vol 6, 1985, pp67-9
55. Bruun, K., (ed.), *Controlling Psychotropic Drugs – The Nordic Experience*, London, Croom Helm, 1983, p255
56. Collier, J., *The Health Conspiracy*, London, Century Hutchinson, 1989, p20
57. Medawar, op cit, pp176-80
58. Ridley, H., *Drugs of Choice*, London, Social Audit, 1986, p8
59. Ramster, D., Barber, A.J., et al, "A policy on benzodiazepines", *Lancet*, 12 Dec 1987, p1406
60. Brahams, D., "Benzodiazepine overprescribing: successful initiative in New York State", *Lancet*, Vol 336, 1 Dec 1990, pp1372-3
61. Shader, R.I., Greenblatt, D.J., et al, "Appropriate use and regulatory control of benzodiazepines", *Journal of Clinical Pharmacology*, Vol 31, 1991, pp781-4
62. Feely, op cit, p301
63. Parish, op cit, p74
64. Matthews, K. and Eagles, J.M., "Which antidepressant?", *British Journal of General Practice*, Vol 41, Mar 1991, pp123-5
65. Breggin, op cit, p194
66. Ibid, p186
67. Matthews and Eagles, op cit
68. Rand, E.H., "Choosing an antidepressant to treat depression", *American Family Physician*, Mar 1991, pp847-54
69. Feely, op cit, p306
70. Breggin, op cit, p188
71. Gilman, A.G., Rall, T.W., Nies, A.S., and Taylor, P., *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, New York, Pergamon Press, (8th edn) 1990, p416
72. BMA and the Royal Pharmaceutical Society of Great Britain, op cit, p156
73. Gilman, et al, op cit, p416
74. BMA and the Royal Pharmaceutical Society of Great Britain, op cit, p151
75. Henry, J. (ed.), *The British Medical Association Guide to Medicines & Drugs*, London, Dorling Kindersley, (2nd edn) 1991, p80
76. Feely, op cit, p307
77. Breggin, op cit, p199
78. Anon., "US group warnings on Prozac", Scrip, No 1533, 20 Jul 1990, p26
79. Anon., "Top 20 products in 1992", *Scrip*, No 1812/13, 16/20 Apr 1993, p29
80. Anon., "US FDA panel on Prozac – effect on litigation", *Scrip*, No 1656, 2 Oct 1991, p21
81. Potter, W.Z., Rudorfer, M.V., et al, "The pharmacological treatment of depression", *New England Journal of Medicine*, Vol 325, 29 Aug 1991, pp633-42
82. Breggin, op cit, p200
83. Levinson, M.L., Lipsy, R.J. and Fuller, D.K., "Adverse effects and drug interactions associated with fluoxetine therapy", *DICP, The Annals of Pharmacotherapy*, Vol 125, Jun 1991, pp657-61
84. Teicher, M.H., Glod, C., et al, "Emergence of intense suicidal preoccupation during fluoxetine treatment", *American Journal of Psychiatry*, Vol 147, 1990, pp206-10
85. Anon., "Prozac claims", *Lancet*, Vol 338, 3 Aug 1991, p307
86. Ahmad, S.R., "USA: fluoxetine 'not linked to suicide'", *Lancet*, Vol 338, 5 Oct 1991, pp875-6
87. Anon., *Scrip*, No 1656, op cit, p21
88. Breggin, op cit, p208
89. Anon., "Dr Moebius attacks Prozac enthusiasm", *Scrip*, No 1517, 25 May 1990, p27
90. Potter, et al, op cit
91. Feely, op cit, p303
92. Breggin, op cit, p211
93. Ibid, pp57-83
94. Morton, I., Hall, J. and Halliday, J., "*Tranquillizers: The comprehensive guide*, London, Bloomsbury, 1992, ppxvi-xvii
95. Laurence, D.R. and Bennett, P.N., *Clinical Pharmacology*, Edinburgh, Churchill Livingstone, (6th edn), 1987, p362
96. Gilman, et al, op cit, p402
97. Wolfe, et al, op cit, p159

Chetley, A. *Problem Drugs*, Amsterdam, Health Action International, 1993

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Subject

Company

Drugs

(names with a capital first letter are brand names, the rest are generic names or therapeutic groups)

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problem drugs

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- ☐ easy to read
- ☐ difficult to follow

Are they:
- ☐ practical
- ☐ not practical enough

Illustrations: are there:
- ☐ too many
- ☐ enough
- ☐ too few

Do you find the language:
- ☐ very easy to understand
- ☐ easy
- ☐ average
- ☐ difficult
- ☐ very difficult

How could the pack be improved?

3. Please tell us how you have used (or plan to use) the pack, which categories of drugs particularly interest you, and whether you would like to contact others doing similar work. Are you interested in becoming involved in HAI activities within your region?

Additional comments:

Useful Addresses

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- Control of Diarrhoeal Diseases (CDD)
- Division of Drug Management and Policies (DMP)
- Expanded Programme on Immunization (EPI)
- Programme for Appropriate Health Care Technology (ATH)
- Special Programme of Research, Development and Research Training in Human Reproduction (HRP)
- Special Programme for Research and Training in Tropical Diseases (TDR)
- Maternal and Child Health and Family Planning (MCH)

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Treatment Guidelines

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Drugs in pregnancy
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Chetley, A., *Problem Drugs,* Amsterdam,
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Appetite stimulants [addendum December 1993]

In November 1993, the US-based company Merck Sharp and Dohme (MSD) announced that it will eliminate the indication of appetite stimulation from all of its cyproheptadine formulations (usually sold under the brand name Periactin) during 1994. It will also withdraw all combinations of cyproheptadine and vitamins, products which the company admits are most commonly used for appetite stimulation.

This is an important, if overdue, step. A key reason for the action was information in this edition of *Problem Drugs* drawing attention to continued promotion of MSD's brand of cyproheptadine for appetite stimulation in commercial prescribing guides in Africa. In press materials for the launch of *Problem Drugs*, Health Action International (HAI) also highlighted promotion of cyproheptadine as an appetite stimulant for children by Merind. Merind was formerly MSD's Indian subsidiary and was partially owned by MSD until 1991, but is no longer licensed to manufacture or sell MSD products.

MSD's move follows nearly a decade of campaigning by HAI and many of its partner organisations around the world. "Appetite stimulants are of no medical value in treating malnutrition. You cannot solve problems caused by poverty with pills," said Roberto Lopez, one of HAI's three international coordinators.

HAI is calling on other companies to follow the example of MSD. It has issued a particular challenge to the Swiss-based company Sandoz, which manufactures another antihistamine, pizotifen, marketed as an appetite stimulant in developing countries.

* * * * *

Appetite stimulants are discussed on p3 (**Introduction**), p12 (**Drugs and children**) and pp106-8 (**Growth stimulants**) of *Problem Drugs*.

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Starting the habit of a lifetime

Infants and children have frequent but not usually serious illnesses. A child's frequent illnesses in the early years are part of a natural process which develops his or her immature immune system. These generally mild infections help to build immunity against common diseases.

Do children need to take a wide range of drugs for these illnesses? On balance, no. However, in general, "too many drugs are given to babies and children."[1] According to the World Health Organization (WHO), two-thirds of all drugs used by children may have little or no value.[2]

The potential dangers of inappropriate drug use are highlighted by the more than 12% of in-patients between 1983 and 1986 at the Hospital Infantil de Mexico who experienced adverse effects to the medication they had received before hospitalisation.[3] In the USA, a 1988 study found that 2% of 6,546 paediatric admissions to hospital wards were due to adverse drug reactions.[4]

One reason for the adverse reactions is that "children are not simply small adults".[5] Their bodies deal with drugs differently from adults. For example, the rate of metabolism is reduced; particularly in infants, the blood-brain barrier is more permeable and the kidney and liver are still developing, so the rate of elimination of drugs is reduced.[6] As a result, infants and children need lower dosages of drugs than adults. The calculation of appropriate dosage usually takes account of both age and weight.[7]

The way children respond to a particular drug can be determined only through research and experience. However, most drugs do not have established doses for infants and children.[8] About three-quarters of the drugs on the market in the USA are either contra-indicated or contain strong precautions for use in children, and nine out of every 10 contain warnings against use by infants and toddlers.[9]

Some common examples of drug misuse in children

- antibacterials for viral upper respiratory infections
- decongestants for colds, resulting in unacceptable adverse effects
- drugs to treat diarrhoea
- oral anti-emetics for vomiting
- antipyretic agents for fever
- tricyclic antidepressants for bed-wetting
- sedatives for sleepless children or those labelled hyperactive
- spasmolytics for abdominal pain
- appetite stimulants

Source: Rylance, G. (ed.), *Drugs for children*, Copenhagen, WHO, 1987. p11

Antidiarrhoeals and cough and cold remedies

Nonetheless, children are often targeted as suitable candidates for drug therapy – especially for the use of over-the-counter remedies for self-limiting conditions such as diarrhoea, cough and colds. Promoting these types of drugs for children also has a longer-term purpose in helping to create a profitable market for medicines in the next generation. Children who grow up with the habit of taking unnecessary medicine to relieve self-limiting illnesses are likely to spend a good deal on drugs within their lifetime.[10]

At least US $1 billion is wasted every year on inappropriate antidiarrhoeal drugs and cough and cold remedies for children. According to WHO, many of these preparations are useless and some are potentially dangerous.[11]

Four million children a year die from diarrhoeal diseases.[12] Oral rehydration therapy plus continued feeding can prevent at least half of those deaths, at a cost of little more than 50 cents a child.[13] "Antidiarrhoeal agents are ineffective and can prolong the diarrhoea. The disease is self-limiting and the real therapeutic goal is simply: *adequate fluid intake*.... Drugs such as loperamide and diphenoxylate must *not* be used in children under 12 years of age."[14]

Another common problem among pre-school children is viral respiratory tract infection. "Most childhood infections are caused by viruses and are self-limiting – that is, the child gets better without any treatment."[15] This is especially true for colds: "uncomplicated head colds, even if causing fever, do *not* warrant pharmacological intervention."[16]

Many cold medicines for children include an antihistamine which can have a sedative effect. They are advertised with a picture of a child sleeping peacefully while a relieved parent, usually the mother, looks on. The overt message is that the mother has lovingly relieved her child's suffering; the hidden message is that the mother can have some peace and quiet by giving her child this type of medicine. Because the antihistamines are often long-acting, their effects can continue for most of the following day, causing the child to have difficulty with muscle control, coordination and balance. Another ingredient included in many popular cold remedies, the decongestant pseudoephedrine, can cause sleep disturbances and nightmares, particularly among young children.[17]

[See the sections on *Antidiarrhoeals*, *Antidiarrhoeals containing antibiotics*, *Hydroxyquinolines*, *Loperamide*, *Diphenoxylate*, and *Cough and cold preparations* for more information.]

Questions for parents to ask about their children's drugs

1. Is this medicine really necessary? Is there a non-drug alternative?

2. What is the name (brand and generic) of the medicine?

3. What does it do? How long will it take for the medicine to work? How will I know that it is effective? What do I do if it does not seem to be working?

4. How much do I give? How often? For how long? Are there special times to give the medicine (for example, before or after meals)?

5. Can my child eat a normal diet? Are there any foods that interact with this drug?

6. Can other medicines be given at the same time?

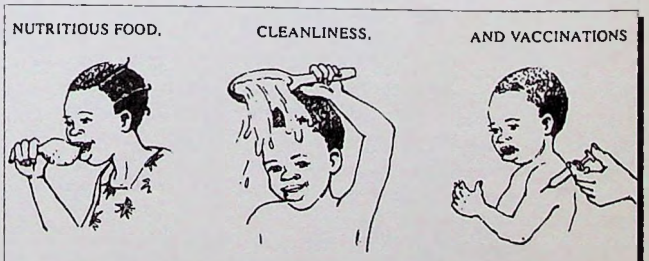
7. Are there any common side effects? Are there any serious but rare side effects? What do I do if any of these occur? Do the benefits outweigh the risks?

8. If my child is allergic to some drugs, will he or she also be allergic to this drug?

9. Do I continue the medicine even if my child gets well before the recommended course is completed? Is there any danger in stopping the medication before the full course is taken? What do I do if one or more doses are missed?

10. How much does this medicine cost? Is there a lower cost but comparable quality generic form available?

Source: adapted from questions prepared by Dr K. Balasubramaniam, reproduced in *Drug Monitor* (Philippines), Vol III, No 12, Dec 1988, p142



Source: Werner, D., Thuman, C. and Maxwell, J. *Where There is No Doctor: a village health care handbook* (revised edn), Palo Alto, the Hesperian Foundation, 1992, p295

However, she points out that psychotropic drugs frequently are used for bed-wetting and insomnia, problems often dealt with by general practitioners. "For both conditions, there are effective behavioural and other treatments, so drugs should never be used as a first line of treatment because of their side effects and the danger of toxicity in overdose (either accidental or deliberate)."[26]

Similar advice is given in the *Australian Prescriber*: "Poor sleeping habits and 'hyperactivity' are often inappropriately treated with drug therapy. Simple counselling, behaviour modification and common sense are the preferred approach."[27]

[See the sections on *Psychotropics* and *Brain Tonics* for more information.]

Appetite stimulants, vitamins and brain tonics

Many parents have unrealistic expectations about the food requirements of their children. According to WHO, they need explanations and reassurance; in most cases children eat normally. However, fear of undernutrition or concern about the common childhood symptom of loss of appetite allows considerable scope for pharmaceutical companies to promote a range of unhelpful products. A particularly disturbing example is the promotion of drugs to stimulate children's appetite. As WHO has pointed out: "There is no evidence that the drugs and mixtures that are proposed as appetite stimulants have any effect on appetite. Therefore, these preparations should not be used."[28]

Packaging for cyproheptadine, an appetite stimulant, promoting use for children, India, 1989-90

Vitamins do have a legitimate role in therapeutics. However, it is a limited role. Children who receive a balanced diet are unlikely to suffer from vitamin deficiencies. Where deficiencies do occur, there is much more need to look at ways to improve the long-term intake of food, while sometimes providing a short-term supplement of one or two particular vitamins. The routine use of multivitamin preparations in children is simply a waste of money. In the UK, for example, vitamins can be prescribed to treat deficiency conditions under the National Health Service, but not as dietary supplements. All of the multivitamin preparations are rated as "less suitable" for prescribing.[29]

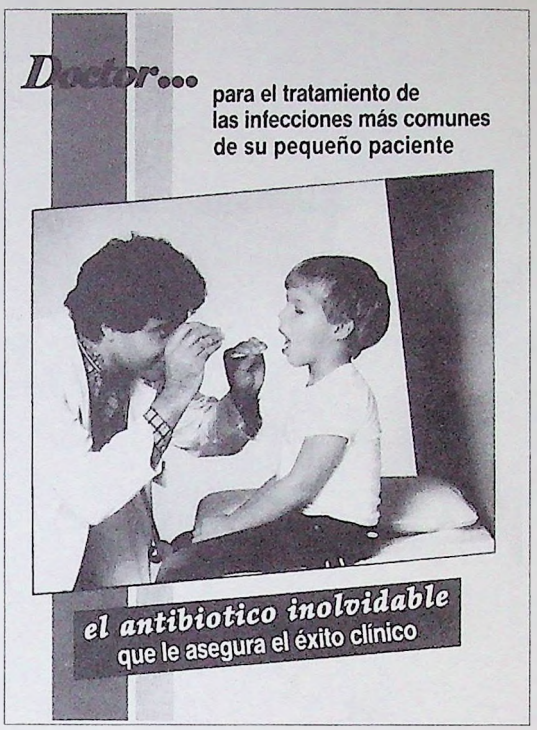
However, children are an obvious target for vitamin manufacturers. In some cases, for example in Asia, companies have gone to extraordinary lengths to ensure that children swallow their vitamin preparations.

In the Philippines in 1989, children were sent home from one primary school with a letter from the school doctor, a prescription for one bottle of the multivitamin preparation, Multi-Sanostol Syrup, made by Byk Gulden and a starter sample of the syrup.[30] In Malaysia, in January 1990, children at a kindergarten in Penang were given samples of Seven Seas multivitamin syrup. A representative of the company producing the vitamins returned to the kindergarten a few days later to sell the children large bottles of the syrup. The children also received an attractive toy as a free gift with every bottle purchased, while the school received a monetary donation for allowing the promotion to take place.[31]

Antibiotics

Antibiotics are among the most frequently prescribed drugs for children. In the USA in 1986, about 35% of the 57.8 million prescriptions for children under the age of three were for antibiotics.[18] However, they are often used inappropriately.[19] They are not useful against viral infections. As viruses cause most childhood diarrhoea and respiratory illness – the two most common childhood illnesses – the use of antibiotics for these conditions is generally unnecessary. In practice, antibiotics are widely used for these conditions. In Brazil, for example, a survey of pharmacies found that pharmacy assistants routinely recommended antibiotics for young children with acute respiratory infections.[20] A survey of pharmacies in Kenya found high levels of antidiarrhoeals containing antibiotics being used indiscriminately.[20a]

[See the sections on *Antibiotics*, *Antidiarrhoeals containing antibiotics* and *Cough and cold preparations* for more information.]



Bad advice to doctors in Peru from Bristol-Meyers Squibb: "Doctor...for the treatment of the most common infections of your little patient the unforgettable antibiotic which assures you clinical success" (advertisement for the antibiotic cefadroxil)

Pain killers and drugs for fever

Most paediatric pain is acute and self-limiting, caused by infection, trauma, surgery, or exacerbation of chronic disease. The recurrent pains of childhood – headaches, abdominal cramps, and limb pains – seldom need a medicine, unless they are caused by an illness or condition requiring drug treatment.[21]

Fever in infants is "generally due to viral infection" and does not usually warrant drug treatment. It can be better managed with simple measures such as undressing the infant, fanning and, if the temperature is very high, tepid sponging.[22]

Fever has generally been regarded as injurious to health. As a result, treating the fever, especially in children, has become routine. However, there is no convincing evidence that naturally occurring fevers do harm. In contrast, studies have clearly shown that fever helps laboratory animals to survive an infection whereas using drugs to prevent the fever increases their death rate. There is also considerable laboratory evidence that a variety of human immunological defences function better at febrile temperatures than at normal ones.[23]

Graham Dukes, editor of the *Side Effects of Drugs Annual*, notes that with children "it is often wise and possible to manage a mild pyrexia [fever] without giving drugs at all; in that respect, some developing countries are the most enlightened of all".[24]

An editorial in the American Academy of Pediatrics journal, *Pediatrics*, about the association of aspirin with Reye's syndrome offered some sound advice generally about caring for children:

> "Physicians caring for sick children need to appreciate that therapeutic interventions, in general, and drugs, in particular, have inherent potential risks that must be weighed against their therapeutic value. In the case of over-the-counter drugs, such as aspirin, it is also incumbent upon physicians to convey this appreciation to their patients."[25]

[See the section on *Analgesics* for more information.]

Psychotropic drugs

Other common problems of childhood such as behaviour and sleep difficulties are frequently considered by parents and doctors to be indications for drug therapy. This medicalisation of aspects and variations of normal growth, behaviour and development is a disturbing trend.

"Are there good indications for the use of psychotropic drugs in children?", asks child psychiatrist, Dora Black, in an editorial in the *British Medical Journal*. Her response is very cautious: "psychotropic drugs should be prescribed sparingly and under the supervision of specialists".

The Philippine letter also cautiously hinted that taking vitamins might improve a child's intelligence. Advertisements during 1989 for another multivitamin syrup, Kiddi Pharmaton, went even further. The advertisements claimed the "body-building, appetite inducing" product – produced by the Swiss company, Pharmaton SA and distributed by Rhone-Poulenc – could also contribute to "better concentration and even improve a child's IQ performance". During 1992, in the UK, three vitamin manufacturers were successfully prosecuted for claiming that their vitamin products could increase children's intelligence.[32]

Other substances are also promoted to improve children's performance at school. In Peru in 1991, the Belgian company, UCB, advertised its piracetam product, Nootropil, as something that would help children with "school difficulties" such as "memory problems, difficulty learning, lack of concentration, intellectual tiredness, poor performance, agitation and irritability".[33] There is no evidence that piracetam can perform any of these miracles.

[See the sections on *Growth Stimulants*, *Vitamins* and *Brain Tonics* for more information.]

Long-term effects

These examples demonstrate some of the "considerable pressure" that parents and prescribers are under from drug companies to use their products. Far too often the result is the selection of "less than optimal or greater than necessary therapy".[34]

Dr Mita Pardo de Tavera, then Secretary of Social Welfare and Development in the Philippines, said in 1988 that she was disturbed to see her medical colleagues prescribing drugs for children that were often unsafe, ineffective or inessential. "Drugs reinforce a curative orientation; yet most childhood health problems are easily prevented through immunisation programmes, proper nutrition, access to safe water and a clean environment and all the other inputs that boil down to one thing: economic development and upliftment.... There is a role for drugs, but it must be taken in context, used appropriately as needed, and not through the creation of artificial demands."[35]

WHO points out that the inappropriate use of drugs for children has both immediate and long-term consequences. For the present, the waste of resources and the potential for unnecessary adverse reactions are both strong arguments to encourage more care in the prescribing of drugs for children. But the unknown psychological and social consequences for children of excessive and inappropriate drug use is a worry for the future as well. "Children may tend to grow up believing that drugs are the solution to many of life's problems."[36]

Recommendations for action

1. Health workers should pause before prescribing any drug for a child and ask themselves whether the drug is really needed and, if it is, whether it is the least toxic, most effective and affordable therapy.

2. Similarly, parents should question health workers about the need for a drug for their children's illness (see the box on page 10 for suggested questions to ask). Before buying an over-the-counter preparation, they should consider whether it is really needed or whether an alternative non-drug solution exists.

3. Governments have a responsibility to ensure that health workers and parents have access to independent information about the correct use of drugs for children.

4. There should be no direct promotion of medicines to children. Governments should also strengthen controls on promotion of medicines aimed at paediatric conditions. They may wish to consider total bans on advertising medicines for children; or they may wish to look at ways in which promotion of medicines for children can be subject to additional restrictions to ensure that exploitation of parental fears is not used to sell drugs.

5. Governments should also review the paediatric medicines on the market with a view to removing those that are hazardous or ineffective.

References:

1. Parish, P., *Medicines: a guide for everybody*, London, Penguin (6th edn, revised), 1989, p35
2. Rylance, G. (ed.), *Drugs for children*, Copenhagen, WHO, 1987, p11
3. Phillips, M., Kumate-Rodriguez, J., Mota-Hernández, F., "Costs of treating diarrhoea in a children's hospital in Mexico City", *Bulletin of the World Health Organization*, Vol 67, No 3, 1989, pp273-280
4. Steele, R.W. and Kearns, G.L., "Antimicrobial therapy for paediatric patients", *Pediatric Clinics of North America*, Vol 36, No 5, Oct 1989, pp1321-49
5. Gaukroger, P.B., "Paediatric analgesia: Which drug? Which dose?", *Drugs*, Vol 41, No 1, 1991, pp52-9
6. Laurence, D.R. and Bennett, P.N., *Clinical Pharmacology*, Edinburgh, Churchill Livingstone, (6th edn), 1987, p140
7. Henry, J. (ed.), *The British Medical Association Guide to Medicines & Drugs*, London, Dorling Kindersley, (2nd edn) 1991, p20
8. AMA, *Drug Evaluations*, Philadelphia, W.B. Saunders Co., (6th edn) 1986, p23
9. Anon., "Paediatric products in US development", *Scrip*, No 1564, 7 Nov 1990, p24
10. Jackson, D.M. and Soothill, R., *Is the Medicine Making You Ill?*, North Ryde, Australia, Angus & Robertson, 1989, p32
11. Anon, "$1 b wasted on useless drugs, says WHO", *Scrip*, 1633, 12 Jul 1991, p22
12. WHO, *The rational use of drugs in the management of acute diarrhoea in children*, Geneva, WHO, 1990, p1
13. UNICEF, *The State of the World's Children 1991*, Oxford and New York, Oxford University Press, 1990, p12
14. Mellis, C.M., "Paediatric prescribing: when is medication needed?", *Australian Prescriber*, Vol 13, No 2, 1990, pp34-6
15. Barry, W. and Hall, J., *Medicines for Children: the comprehensive guide*, London, Bloomsbury, 1990, px
16. Mellis, op cit
17. Grant, R., *Which? Medicine*, London, Consumers Association and Hodder & Stoughton, 1992, p46
18. Levy, S., "Starting life resistance-free", *New England Journal of Medicine*, Vol 323, No 5, 2 Aug 1990, pp335-7
19. Parish, op cit, p35
20. Misago, C., and Fonseda, W., "Antimicrobial drugs advised in pharmacies in Brazil for children with acute respiratory infections", *Lancet*, Vol 338, 14 Sep 1991, p702

20a. Yudkin, J.S., "Dispensing of inappropriate medicines for diarrhoea", *Lancet*, Vol 335, 31 Mar 1990, p803

21. Maunuksela, E-L. and Olkkola, K.T., "Pediatric pain management", *International Anesthesiology Clinics*, Vol 29, No 2, May 1991, pp37-55
22. Mellis, op cit
23. Kramer, M.S., Naimark, L.E., et al, "Risks and benefits of paracetamol antipyresis in young children with fever of presumed viral origin", *Lancet*, Vol 337, No 8741, 9 Mar 1991, pp591-4
24. Dukes, M.N.G., (ed.), *Side Effects of Drugs Annual 11*, Amsterdam, Elsevier, 1987, p79
25. Kauffman, R.E. and Roberts, R.J, "Aspirin use and Reye syndrome", *Pediatrics*, Vol 79, No 6, Jun 1987, pp1049-50
26. Black, D., "Psychotropic drugs for problem children: need specialist supervision", *British Medical Journal*, Vol 302, 26 Jan 1991, pp190-1
27. Mellis, op cit
28. Rylance, op cit, p48
29. BMA and the Royal Pharmaceutical Society of Great Britain, *British National Formulary*, London, BMA and The Pharmaceutical Press, No 23, Mar 1992, pp339-44
30. Anon., "Children's vitamin preparations: kidding the kids and their parents", *Drug Monitor* (Philippines), Vol IV, No 8, Aug 1989, pp109-10
31. Zaini, J., "Pushing children's vitamins", *HAI News*, No 51, Feb 1990, p1
32. Anon., "UK vitamin manufacturer fined over IQ claims", *Scrip*, No 1763, 20 Oct 1992, p9
33. Lopez Linares, R. and Phang Romero, C., *Promoviendo la Salud o Los Negocios? Un análisis de la promoción farmacéutica*, Chimbote, Acción para la Salud, 1992, p8
34. Rylance, op cit, p6
35. Pardo de Tavera, M., "Children's Drugs in the Philippines", *Drug Monitor* (Philippines), Vol III, No 12, Dec 1988, p131-2
36. Rylance, op cit, pp11-12

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Disturbing a delicate balance

Women occupy a dual position in the use and delivery of health care. Women make more use of health care services and take more medicine than men.[1] As individuals, women have distinct and significant health needs, related in part to reproduction. As "agents" they are the informal providers of health care in the family and form the majority of professional health workers in the community.[2]

However, although women are both the major users and major providers of health care, they are seldom in a position to determine the priorities.[3] Most health care systems are male-dominated in terms of policy and decision making, and effectively exclude women from positions of power.[4] Policy makers have designed health care systems primarily for the convenience of doctors (who are predominantly male), hospitals and the medical industries.[5]

The model of a male life cycle is all too often taken as a norm. When this is applied to women, it is no wonder that a large number of natural and normal processes become diagnosed as "abnormal" and, as a result, have a barrage of drugs thrown at them.[6] The pharmaceutical industry has a vested interest in helping to maintain this idea and uses its marketing strategies to promote drugs as a solution for these "health problems."[7]

Effects of drugs on women

Poor information about the effects of medication on women is another concern. Sexual prejudice helps determine research policies and biases some research results. For example, in a study of more than 17,000 people in the UK to determine the possible adverse effects of drugs taken for high blood pressure, only men were asked whether the drugs affected their sexual desire.[8]

Women metabolise drugs differently from men. In part this is due to weight differences between men and women and in part due to hormonal differences.[9] Another factor can be undernutrition or malnutrition. In developing countries, malnutrition is far more prevalent among women than men, a gender difference that often starts in childhood.[10]

A 1992 report from the General Accounting Office in the USA called for the inclusion of more women in

clinical trials for drugs and more analysis of potential gender differences in safety and efficacy of drugs. Only 12% of 53 drugs approved in recent years in the USA had special studies to look at hormonal interactions or interactions with oral contraceptives. Drug safety data were analysed by gender for only 54% of the drugs and efficacy was analysed by gender in only 43%.[11]

Drug safety

Drug safety has been a major concern for women over the past three decades. The tragedy of thalidomide in the 1960s brought home the high risk of taking drugs in pregnancy. Most of the major drug regulatory agencies in industrialised countries were either established or strengthened as a result. Extensive testing is now done to identify the drugs most likely to cause fetal defects. Even so, as the American Medical Association has pointed out: "for many drugs, particularly new ones, little or no information is available on use during pregnancy."[12]

There have also been tragedies with older drugs that are now rarely used in industrialised countries, but which still pose a problem in developing countries.

Diethylstilboestrol (DES), a synthetic oestrogen, was widely used to prevent miscarriage but was found to be ineffective and unsafe. Prenatal DES exposure has been linked to malformations of the reproductive organs in both women and men, which can lead to problems in pregnancy and infertility. A rare form of vaginal cancer – clear-cell adenocarcinoma – occurs in about one in every 1000 women exposed prenatally. Women who took DES during pregnancy also have an increased risk of breast cancer. Experts now agree that there is no indication for the use of DES or any oestrogen in pregnancy.[13]

High-dose oestrogen and progestogen (EP) drugs have enjoyed wide popularity in many developing countries as a test for pregnancy. However, the World Health Organization (WHO) points out that as a pregnancy test, EP drugs are unreliable and there is a risk of malformations if they are used during pregnancy.[14]

Despite the lessons of the past, there is still evidence of unnecessarily high intake of drugs by pregnant women. Some of this can be attributed to women not knowing the full dangers of taking drugs during pregnancy, but in part it is also due to routine medical practice. Most women who go to hospital in the UK to have a baby are given some form of sedation the night before delivery. Clinical pharmacologist, Joe Collier, asks: "Who are the drugs really for – the mother-to-be, her baby, or the medical staff who want a quiet night?"[15]

[See the sections on *Drugs in Pregnancy, DES,* and *EP Drugs,* for further information.]

Questions for women to ask about drugs

1. What is the name (brand and generic) of the drug?
2. Is this drug really necessary? Is there a non-drug alternative?
3. What does it do? Does it cure the disease or only treat the symptoms? How long will it take for the drug to work? How will I know that it is effective? What do I do if it does not seem to be working?
4. I am pregnant, breastfeeding or planning to become pregnant. Should I use this drug?
5. I use oral contraceptives. Will this drug affect the efficacy of the contraceptives or interact with them in any other way?
6. Can I take other drugs at the same time? Can I drink alcohol? Are there foods I should avoid?
7. What are the common side effects? Are there any rare serious side effects? What should I do if I experience side effects?
8. Is there any information available on the long-term effects of using this drug?
9. If I am being given this drug to help prevent a disease I may get later on, are there other alternatives that may make me less likely to develop the disease?
10. Is it possible to become dependent on this drug?

Medicalisation of life events

Generally, there has been an increasing tendency to medicalise women's lives. More and more, women are expected to visit the doctor to deal with normal aspects of life such as contraception, pregnancy and childbirth. Indeed, the whole time from menstruation to menopause "is now often discussed as though it were a disease".[16] Drug treatments are offered for hormonal changes related to the menstrual cycle, such as premenstrual tension. Even the menopause is being redefined as a deficiency state.

On the whole, more women face poverty, economic dependence, or poor housing and living conditions

than men, and more women are the primary caregivers for young children and the elderly[16a], leading to a heavy overall workload and considerable stress. Although the real solutions to these problems are social, political and economic, it is no wonder that the marketing of anti-anxiety drugs and anti-depressants is primarily targeted to women. For every benzodiazepine tranquilliser prescription written for men in the UK, three are written for women.[17] Similar patterns exist in other countries.

One of the classic advertisements that helped to entrench the use of tranquillisers in women was by Roche for its Librium (chlordiazepoxide). The advertisement shows two hands: one of a woman, the other of a man. The man – a doctor – is taking the woman's pulse. And the headline reads: "Whatever the diagnosis... Librium".[18]

[See the section on *Psychotropics* for more information.]

Hormones

In the 1960s, women were promised freedom from unwanted pregnancies if they used hormonal oral contraceptives. In the 1990s, many of those same women are being promised freedom from the effects of the menopause if they continue on a daily dose of hormones. Those hormones have been linked to a variety of side effects that can cause women discomfort and interfere with the quality of their lives. More worrying is the possibility that hormones may cause some forms of cancer or other long-term effects. An American biologist describes the use of hormones as being little more than an experiment. She says "the gynecologist/obstetrician is probably more of a medical empiricist than any other specialist; that is, the gynecologist administers hormones as a treatment because they work and not because there is a clearly defined understanding of their action in the body."[19] Certainly, too little is known about the long-term effects.

Contraceptives

Having access to safe and effective methods of contraception is important for women. Women in a village in Indonesia explained what they wanted in a family planning method: "We would gladly accept family planning provided that it doesn't interfere with our work, or do us any permanent harm, or be against our religion. It also has to be explained to us by a woman, who will examine us if necessary and keep it a secret. It should also cost very little money."[20] These simple and clearly stated criteria are seldom met.

Women, particularly in developing countries, are poorly informed about the pros and cons of contraception. Without proper information, women become suspicious that they are being manipulated.

Another reason women reject the current selection of contraceptive methods is that it has not been designed with their needs in mind. For example, women may not agree that a small increase in effectiveness is worth the trade-off of a higher frequency of menstrual cycle disturbances and other side effects. Demographers and family planning workers may also be more concerned than individual women about avoiding methods with the potential for "user failures".[21]

[See the sections on *Contraceptives*, *The Pill*, *IUDs*, *Injectables*, and *Implants*, for more information.]

Menopause and hormone replacement therapy

"Menopause is not a disease, but a life-cycle transition," says medical anthropologist, Margaret Lock.[22] It is a time of change in a woman's life and, for most women, it is accomplished with minimal discomfort and without the need for medical intervention.[23]

The pharmaceutical industry has a different opinion. It promotes hormone replacement therapy (HRT) – oestrogen (often with progestogen) – to deal with the symptoms of the menopause. In the USA, Ciba-Geigy ran ads in women's magazines for its transdermal oestrogen preparation, Estraderm, that talked about two common perceptions of the menopause: "No man in his right mind would be interested in a menopausal woman" and "you'd better leave sports to the youngsters". The advertisement concluded that by using Estraderm, "the change of life doesn't have to change yours". The implication in this advertisement and many others directed at consumers or doctors is that without hormones, women will experience serious loss. Most of the advertisements focus attention on a woman's looks and emotions rather than on the medical effects of the drugs.[24]

As with hormonal contraceptives, little is known about the effects of long-term use of hormones during and after the menopause. There is a higher rate of endometrial cancer among women who have used oestrogen therapy. There is also doubt about the benefits of hormone therapy. This, coupled with the lack of good research into alternatives, leaves both women and doctors with little valid information to help them decide whether therapy is needed and if so, which type.

[See the section on *HRT* for more information.]

Promoting drugs

Because women are the "pathway" for medicines within the family and make the decisions about what drugs to buy,[25] they are frequently the target of promotional campaigns for over-the-counter (OTC)

drugs. A large proportion of OTC drugs are aimed at children, but the promotion is meant to tug at the emotions of the parents, particularly mothers. Advertisements for vitamins, tonics, appetite stimulants, cough and cold remedies and antidiarrhoeals, often show a woman in a caregiving role, doting on a child who is making a rapid recovery because of the drug *she* has given. Some promotional campaigns are for products for the women themselves to use to live up to the image of beauty, youth and vitality that is portrayed. Vitamins, slimming aids, skin conditioners all promise much. But if the products fail to meet the promises, and the women suffer from tiredness or menstrual pain, for example, there are more solutions: vitamins again, various tonics, and analgesics and NSAIDs for the pain. One classic advertisement from the Philippines for G.D. Searle's Dramamine (dimenhydrinate – a drug to treat motion sickness) featured a housewife who was sweeping her yard when she became dizzy. In the comic strip used to promote the drug, her neighbour comes to the rescue and advises her to take Dramamine: "Rest and Dramamine. That's all she needs." It is an extraordinary idea that an anti-nausea drug can deal with the fatigue of housework.[26]

In addition to products for self-medication, there are hormone preparations and antidepressants that doctors can prescribe to deal with life's problems. Because women are the major consumers of medicines, much promotion sent to doctors promotes prescription-only drugs specifically for women. Much of this material has been found to emphasise negative stereotypes. These include the idea that women can't cope, that they are not very intelligent, that they can be a real nuisance to others, and that biology determines their destiny. The basic idea was conveyed by one early advertisement for hormone replacement therapy that had a headline: "Something is terribly wrong".[27] In the Philippines, Searle relied on the comic strip approach with a cartoon ad for doctors in 1988 that promoted its antidiarrhoeal, Lomotil (diphenoxylate). The image in the cartoon is of a woman who could not cope, not even on her wedding day. Instead, it was up to Lomotil to save the day.[28] A cartoon advertisement from Belgium in 1992 shows a male doctor being overwhelmed by his complaining female patient who has every gastrointestinal symptom imaginable. The solution being offered to the doctor is Boehringer Ingleheim's Tranquo-Buscopan – a combination product that contains an anti-spasmotic (hyoscine butylbromide) and a tranquilliser (oxazepam).

In Peru, in 1991, Schering promoted its ergot derivative, Dopergin (lysuride), for inhibition of lactation. The advertisement showed five slender women, and described the product as "the most potent inhibitor of prolactin in the clinic". The implicit message, suggested by the photographs of the women was that to have a slender figure, women should stop breastfeeding – a

The woman who can't cope, in Searle's promotion of diphenoxylate (Lomotil), PIMS, the Philippines, Dec 1988

"Doctor! I am in such pain...bla bla bla...cramps...bla bla bla constipation... bla bla bla...Oh Doctor...straining...bla bla...diarrhoea...bla bla bla bla...So much pain...bla bla bla...bad indigestion...bla bla bla...stomach ache bla bla bla and bla bla bla...rumbling stomach...a knot in my bowels bla bla bla bla...feel very bloated bla bla bla stomach ache bla bla bla."
Boehringer Ingelheim ad for Tranquo-Buscopan, Artsenkrant, Belgium, Sep 1992

message that plays into the stereotype that breastfeeding can harm the figure, but that bears little regard to reality or to the public health benefits for mother and child alike that can come from breastfeeding.[29]

A majority voice which needs to be heard

Women make up the majority of health care consumers and health care workers and should have the major voice in determining health and medical care policy. Local communities, individual health care facilities, and national governments all need to explore ways in which women can have a much greater say in how health care is organised. One important aspect is looking at ways in which a more rational use of drugs for women can be achieved.

Recommendations for action

1. More research is needed into the effects of drugs on women, with particular attention to their efficacy and safety.

2. There should be greater consultation with women on the research needs for contraceptives and for products specifically meant for women.

4. Women need better information about drugs, particularly their effects during pregnancy and while breastfeeding.

5. Stronger controls are needed over the way drugs are promoted to women, particularly promotion which contributes to unnecessary medicalisation of women's lives and promotion of psychotropic drugs which targets women.

6. Controls are needed over the way in which images of women are used to promote drugs.

References:

1. Wolffers, I., Hardon, A., and Janssen, J., *Marketing Fertility: Women, Menstruation and the Pharmaceutical Industry*, Amsterdam, WEMOS International Group on Women and Pharmaceuticals, 1989, p9
2. Baile, S., "Women and health in developing countries", *OECD Observer*, No 161, Dec 1989-Jan 1990, pp18-20
3. Ibid
4. Collier, J., *The Health Conspiracy*, London, Century Hutchinson, 1989, p6-8
5. Phillips, A., Rakusen, J. (eds) and the Boston Women's Health Collective, *The New Our Bodies, Ourselves* (2nd UK edition), London, Penguin Books, 1989, p608
6. Rochon Ford, A., "Hormones: getting out of hand", in: McDonnell, K. (ed.), *Adverse Effects: Women and the Pharmaceutical Industry*, Penang, IOCU, 1986, pp27-40
7. Querubin, M.P. and Tan, M.L., "Old roles, new roles: women, primary health care, and pharmaceuticals in the Philippines", in: McDonnell, op cit, pp175-86
8. Collier, op cit, pp9-10
9. Grossman, W., "Not in my image", *New Scientist*, 27 Mar 1993, p37
10. Jacobson, J.L., *Women's Reproductive Health: the silent emergency*, (Worldwatch Paper 102), Washington, Worldwatch Institute, 1991, pp18-20
11. Anon., "GAO study on women in clinical trials", *Scrip*, No 1769, 10 Nov 1992, p17
12. AMA, *Drug Evaluations*, Philadelphia, W.B. Saunders Co., (6th edn) 1986, p42
13. Ibid, p701
14. WHO, *The Effect of Female Sex Hormones on fetal Development and Infant Health*, Technical Report Series, No 657, Geneva, 1981
15. Collier, op cit, p15
16. Phillips, et al, op cit, pp612-3
16a. Smyke, P., *Women and Health*, London, UN Non-Governmental Liaison Service and Zed Books, 1991, pp25-27
17. Collier, op cit, p8
18. Medawar, C., *Power and Dependence*, London, Social Audit, 1992, p85
19. Biologist Ethel Sloane, quoted by Rochon Ford, op cit, pp27-40
20. Warren, M., "Better safe than sorry", *New Internationalist*, Oct 1987, p22
21. Ibid
22. Lock, M., "Contested meanings of the menopause", *Lancet*, Vol 337, 25 May 1991, pp1270-2
23. National Women's Health Network, *Taking Hormones and Women's Health: Choices, Risks, Benefits*, Washington, 1989, pp2 and 6
24. US Congress, Office of Technology Assessment, *The Menopause, Hormone Therapy, and Women's Health*, OTA-BP-BA-88, Washington, US Government Printing Office, May 1992, p71
25. McDonnell, op cit, p3
26. Querubin and Tan, op cit, pp175-86
27. Rochon Ford, A., "In poor health", *Healthsharing*, Winter 1986, pp13-17
28. Searle advertisement, *PIMS*, Dec 1988, p237
29. Lopez Linares, R. and Phang Romero, C., *Promoviendo la Salud o Los Negocios? Un análisis de la promoción farmacéutica*, Chimbote, Acción para la Salud, 1992, p12

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1D. Drugs and the elderly

Too often, too many, too much

"One of my most lasting memories of medical school in Scotland was our teaching in drug prescribing.... Again and again, terribly sick elderly people would be admitted. The unfortunate medical students, sent off to examine the frail old folk, came back thoroughly puzzled, since the pattern of symptoms and signs didn't fit one of our textbook diseases.... After a few days these people, who looked dreadful when they were carried in, walked out well. All that had happened in between was that all their drugs had been stopped and only those which seemed absolutely necessary represcribed. The combined actions and interactions of the four, six or even nine preparations they'd been swallowing had poisoned them."
– Dr Norman Swan, producer and presenter of The Health Report on ABC Radio in Australia[1]

Health problems are highly prevalent among the elderly. Around 80% have one or more chronic diseases.[2] As a result, the elderly consume a high proportion of drugs. The sale of pharmaceuticals to elderly patients for outpatient use in the USA was worth $4.6 billion in 1988 and is expected to reach $10.1 billion by 1995.[3] In both the UK and the USA, the elderly consume at least 30% of all prescribed drugs.[4] In the USA, the average person over 65 receives 10.7 new and refill prescriptions a year.[5] In the UK, 70% of a representative sample of people over 65 had been prescribed drugs, and 60% of the sample had taken one or more prescribed drugs in the 24 hours before being interviewed. On average, 2.8 drugs had been prescribed per person. Almost one in three of the prescriptions was considered "pharmacologically open to question".[6] In Italy, 40% of people over 70 take between four and six drugs daily, and 12% take more than nine.[7]

Adverse drug reactions

This high consumption of drugs leads to a large number of adverse drug reactions (ADRs). "All the consequences of polypharmacy – increased costs, ADRs, and drug abuse and misuse – are more likely to occur in the elderly than in any other age group."[8]

A study in the UK found that ADRs were solely or partly responsible for 10% of admissions to geriatric units.[9] In Canada, an estimated 20% of elderly people admitted to acute care hospitals in one province had prescription drug-related complications.[10] There is, however, some debate about whether the disproportionate number of ADRs is directly age-related. According to Frank Young,

In the USA:
1 out of every 6 people is over 60
but they consume:
1 out of every 3 tranquillisers
1 out of every 2 sleeping pills
1 out of every 3 antidepressants
2 out of every 3 antihypertensives
2 out of every 5 gastrointestinal drugs

Source: Wolfe, S.M., Fugate, L., et al, *Worst Pills Best Pills*, Washington, Public Citizen Health Research Group, 1988

Promotion of the NSAID etodolac (Lodine) for the elderly, Wyeth-Ayerst, American Journal of Medicine, *Aug 1991*

former Commissioner of the US Food and Drug Administration (FDA), it is more likely to be related to the number of drugs taken by the elderly.[11]

Although drugs can play a necessary and valuable role both for the health and the quality of life of the elderly, too often the risks of adverse effects are downplayed in promotional materials from pharmaceutical companies. For example, some of the advertising that Wyeth-Ayerst used to launch its new non-steroidal anti-inflammatory drug (NSAID), Lodine (etodolac), in the USA in 1991 proclaimed that it was "well-tolerated in adults of all ages". It went on to say that "in patients 65 years and older" there were no substantial differences in the side effects profile compared with the general population. In the small print of the advertisement, however, was the standard comment that etodolac, like other NSAIDs, could cause kidney failure, and that the elderly were among those at greatest risk.[12] The "well-tolerated" headline also detracts from the available evidence that etodolac causes "the usual spectrum of upper GI [gastrointestinal] toxicity".[13]

As a study released by the US Department of Health and Human Services in 1989 puts it, "a major factor in the number of adverse drug reactions among the elderly is their doctors' over-reliance on promotional materials provided by the drug manufacturers".[14]

Table 1D-1
Drugs most frequently associated with adverse effects in the elderly

Type of drugs	% of total ADRs
antihypertensives	13.1
antiparkinson drugs	13.0
corticosteroids	12.3
psychotropics	12.1
digitalis	11.5
insulin and hypoglycaemics	9.2
diuretics	8.0

Note: These figures are based on a multicentre study of geriatric hospital admissions for acute care.
Source: Denham, M.J., "Adverse drug reactions", *British Medical Bulletin*, Vol 46, No 1, 1990, pp53-62

1.5 million elderly people have been on minor tranquillisers daily for one year or more, and more than 500,000 elderly people use sleeping pills daily for one month or more. In both cases, there is no evidence that they are effective for continuous, long-term use.[27]

The benzodiazepine tranquillisers have long been linked with adverse effects on psychomotor tasks, learning and memory in elderly people.[28] "Sleeping pills, sedatives or tranquillisers in 'average' doses may make the elderly person confused and unsteady; a benzodiazepine sleeping drug which would be excreted by most patients within eight hours may 'hang over' the whole of the next day."[29]

Psychotropic drugs have consistently been shown to be associated with an increased risk of falls in the elderly. Diazepam, in particular, was found to have a high association with falls, leading researchers to suggest that it should not be used in the elderly.[30]

[See the section on *Psychotropics* for more information.]

NSAIDs

In the UK, about 2,500 cases of bleeding or perforated peptic ulcers caused by NSAIDs are reported to the Committee on Safety of Medicines each year. They are predominantly in people who are over 60 years of age. However, most of the people receiving these drugs are not suffering from one of the inflammatory forms of arthritis, such as rheumatoid arthritis or gout, where NSAIDs are of some benefit. More than three out of every four people receiving NSAIDs are elderly, "an age when inflammatory joint disease is relatively uncommon".[31]

Although there was initially considerable enthusiasm for the use of NSAIDs, the adverse effects of these drugs, sometimes with fatal consequences among the elderly, has begun to instil some caution in their use:

> "All non-steroidal anti-inflammatory drugs (NSAIDs), particularly those with prolonged half-lives, should be used with caution in the elderly."[32]

> "Use of aspirin and other NSAIDs should be avoided, if possible, in older patients with a history of upper gastrointestinal haemorrhage."[33]

For osteoarthritis, which is more prevalent among the elderly and is less of an inflammatory condition, NSAIDs generally only provide some symptomatic relief. They should be used "only as required to supplement a baseline simple analgesic such as regular paracetamol".[34]

[See the section on *NSAIDs* for more information.]

Prescribing for the elderly – a checklist

- ☐ *Drug history:* What other drugs (including over-the-counter preparations) is he or she taking? What other drugs or therapy have been tried for this condition?
- ☐ *Symptoms:* Could the symptom(s) he or she is suffering from be a side effect of a drug being taken, or the effect of coming off a drug?
- ☐ *Necessity:* Is the drug really necessary? Is there a better non drug alternative?
- ☐ *Interaction:* Is there likely to be any interaction with other drugs being taken or with food?
- ☐ *Add one/remove one:* If one drug is being added to a therapeutic regimen, is it also possible to withdraw one, so as not to increase the number of drugs being taken?
- ☐ *Dosage:* Is the dose appropriate?
- ☐ *Formulation:* What is the best formulation to make the drug easier to use?
- ☐ *Appropriate use:* Is he or she likely to take the drug at the right time in the right amounts? Does he or she need more information?
- ☐ *Stop the drug:* When should the drug be stopped? Is there a good follow-up plan to ensure that the drug is effective and does not cause adverse effects?

Antibiotics

The elderly have an increased risk of infections,[35] and a higher mortality rate from those infections than younger adults,[36] leading to a more frequent use of antibiotics. Normal age-associated decline in kidney function means that the time it takes for the body to eliminate an antibiotic (or other drug excreted through the kidney) increases. Therefore, the elderly usually require lower dosages. For most antibiotics, however, dosage guidelines do not as yet incorporate a reduction in dosage for the elderly.[37] Unless dosages are reduced, there is a risk that drugs may accumulate in the body, reaching toxic levels. In addition, antibiotic side effects may be more common in the elderly, and interactions between antibiotics and other drugs may be more marked due to declining liver function.[38]

The Australian Drug Evaluation Committee ruled in 1990 that product information for co-trimoxazole preparations (trimethoprim and sulphamethoxazole) should warn of the increased risk of serious adverse effects in the elderly and discourage the use of the product in this age group.[39]

The FDA has proposed that manufacturers should provide doctors with clear information that reflects all available knowledge about the effects of prescription drugs in elderly people. Where such data are lacking for a particular drug, manufacturers should indicate clearly that such information is not available.[15]

Just as the tragedy of thalidomide led to more care in the prescribing of drugs for pregnant women and better drug testing to establish potential risks, it took a serious event for changes to occur regarding drugs for the elderly. The death of elderly people who used the NSAID benoxaprofen (Opren/Oraflex) in the early 1980s led to the drug's withdrawal. More importantly, it led to the establishment of more precise guidelines from regulatory authorities about the need for new drugs to be evaluated in the elderly populations for which they will be prescribed rather than only in young volunteers.[16]

Changes affecting drug metabolism

Taking too many drugs is only part of the problem. Even a single drug can have a more dramatic effect among the elderly because of several physical changes that affect the way the elderly metabolise drugs. These include:

- reduced blood flow and motility in the gastrointestinal tract, making absorption of drugs slower;
- decreased body weight, less body water, less protein in the blood, so there is a likelihood of greater concentration of many drugs, particularly those that are water soluble;
- increased body fat, so fat-soluble drugs have a lower concentration;
- reduced blood flow to and enzyme activity in the liver, allowing some drugs to pass into the blood stream in greater concentration and to stay in the blood stream longer;
- reduced kidney function, so that drugs are not eliminated from the body as quickly; and
- fewer receptors and transmitters in the brain and central nervous system, so that drugs that act on the central nervous system can have a more pronounced and long-lasting effect.[17]

Because there is a greater risk of drugs accumulating in the body, the elderly need "careful tailoring" of drug dosages to their particular needs, their state of health and their social circumstances. Failure to provide this personalised prescribing can lead to tragic results. A person who becomes confused on tranquillisers may be considered senile and admitted to a geriatric unit, where more drugs are administered to control the confusion. Drugs used to reduce blood pressure lower the volume of blood reaching the heart and brain, which again can stimulate symptoms of senility and put the person at risk. Diuretics lead to more frequent emptying of the bladder and can stimulate incontinence in the elderly.[18] Diuretics are frequently overprescribed in the elderly.[19]

In very old people, "manifestations of normal ageing may be mistaken for disease and lead to inappropriate prescribing". For example, drugs such as prochlorperazine are commonly misprescribed for giddiness due to age-related loss of stability. Not only is such treatment ineffective but the user may experience serious side effects such as drug-induced parkinsonism, postural hypotension, and mental confusion.[20]

Ensuring appropriate use

Another factor which can lead to complications in therapy and possibly ADRs is a person's failure to take medicines appropriately. This is a problem common to patients of any age. In the elderly, it may be exacerbated by poor memory, poor hearing and vision, difficulty in opening containers, and having to cope with complex dosage regimes.[21]

The pharmaceutical industry often promotes fixed dose combination drugs as a way of achieving compliance among the elderly. Popular combinations include antihypertensives with diuretics. Such products should never be the first choice in treating high blood pressure. If non-drug therapy of diet, weight loss, exercise and lower salt intake has not achieved the desired result, a low dose of a simple diuretic is often sufficient. If a second drug is needed (usually a beta-blocker or a calcium-channel blocker), the two drugs should be given separately in order to adjust the doses of both until the right balance is found. *If* the doses that are needed to control blood pressure are those found in a combination product, *then* this product can be used to simplify medicine regimens.[22] "Drug therapy should be tailored to the individual patient and increased in a stepped fashion, with a maxim of 'start low and slow' kept in mind to reduce the incidence of side effects and make treatment more acceptable."[23]

In general, fixed combinations of drugs should be used only when they are logical, have been well studied, and they either improve tolerance or efficacy. Few fixed combinations meet this standard.[24]

Deciding when to stop a drug

There is now sufficient evidence that long-term treatment is not necessary for many people taking hypnotics and other psychotropics, diuretics, digoxin, and NSAIDs. Repeat prescribing without review is no longer an acceptable practice.[25]

Psychotropics

Psychotropic drugs are frequently prescribed for the elderly. They can cause distressing side effects. In the UK, one study found that half of the elderly patients admitted to the medical wards of a hospital were taking benzodiazepine tranquillisers that had been prescribed by their general practitioner.[26] In the USA,

Aminoglycosides are also generally used with great care in the elderly because of the risks of kidney damage and hearing loss. Both are problems which are already more common in the elderly.[40]

[See the section on *Antibiotics* for further information.]

Drugs and dementia

With more than 50 million people worldwide over the age of 65 currently estimated to be suffering from dementia, analysts predict that the worldwide market for "cognitive enhancers" to treat dementia will be over US $1.5 billion by the year 2000.[41]

A number of "cerebral" vasodilators and similar drugs (often called nootropics) are currently in wide use for the treatment of mental failure in the elderly. Goodman and Gilman's pharmacology textbook says "the case for clinical efficacy is unimpressive" for these products in treating dementia.[42] According to the *British National Formulary* (BNF), although some improvements in performance of psychological tests have been reported, "the drugs have not been shown clinically to be of much benefit in senile dementia."[43]

Nonetheless, products such as these are widely promoted, particularly in developing countries, for a range of symptoms associated with dementia and old age. The Medical Lobby for Appropriate Marketing (MaLAM) has regularly challenged pharmaceutical companies to defend the claims made for the various "brain tonics" on the market. To date, the industry has been unable to produce much evidence in its defence.[44]

On the other hand, drugs themselves are often linked with inducing dementia. Psychotropic drugs – particularly sedatives and hypnotics – antihypertensives, anticonvulsants, and digitalis are those that have most frequently been associated with reversible dementia.[45]

[See the section on *Brain Tonics* for further information.]

Cautious prescribing

The adverse effects resulting from the attempt "to rectify all age-induced and disease-induced disorders with a panoply of polypharmaceutical remedies" are often the last straw that makes it impossible for an elderly person to continue to lead a reasonably independent life.[46]

Some simple precautions in the prescribing and use of drugs can help prevent this. The checklist in the box on page 24 provides some ideas for prescribers to bear in mind.

Principal among these is the need to check whether a drug is really needed. "It is important to be sure in each case that the condition being treated really justifies drug treatment *in that patient at that time.*"[47] Side effects of one drug should rarely (if ever) be treated with another.[48]

Next is the need to limit drugs to as few as possible, at the lowest possible dose. "The fewest possible drugs should be given to elderly patients, and in the minimum dosage which is effective for them, even if this is far less than the 'average'."[49]

It is "a sensible policy" to prescribe from a limited range of drugs and to be thoroughly familiar with their effects in the elderly.[50] This means being critical of the promotional claims made by the pharmaceutical industry about drugs aimed at a variety of conditions in the elderly.

Finally, there is the question of knowing when to stop. Elderly people need careful monitoring to ensure that they are not being kept on drugs unnecessarily.

Recommendations for action

1. Meeting the special needs of the elderly should be seen as an important element of developing drug information for both prescribers and consumers.

2. Prescribers should use considerable caution when selecting a drug to treat a condition in the elderly, making sure the drug is necessary, that the lowest possible dosage is used, and that it is well tolerated.

3. Elderly people and/or their carers should question carefully the need for all medicines and encourage doctors and health workers to explore non-drug therapies wherever possible.

4. Governments and health authorities need to ensure that better information is available for the public, prescribers and pharmacists about the risks of unnecessary drug taking among the elderly.

5. Governments should carefully monitor claims made about the use of drugs in the elderly.

References:

1. Jackson, D.M. and Soothill, R., *Is the Medicine Making You Ill?*, North Ryde, Australia, Angus & Robertson, 1989, px
2. Zazove, P., Mehr, D.R., et al, "A criterion-based review of preventive health care in the elderly: Part 2. A geriatric health maintenance program", *Journal of Family Practice*, Vol 34, No 3, 1992, pp320-47
3. Anon., *Growing Opportunities for Geriatric Pharmaceuticals*, New York, MIRC, 1989
4. Bird, H.A., "Antirheumatic drugs in the elderly", *Annals of the Rheumatic Diseases*, Vol 49, 1990, pp1022-4; Lowenthal, D.T. and Nadeau, S.E., "Drug-induced dementia", *Southern Medical Journal*, Vol 84, Suppl. 1, May 1991, pp1S-24--1S-31
5. Cummings, D.M. and Uttech, K.M., "Antibiotics for common infections in the elderly", *Primary Care*, Vol 17, No 4, Dec 1990, pp883-903
6. Anon., "Elderly people their medicines and their doctors", *Drug and Therapeutics Bulletin*, Vol 28, No 20, 1 Oct 1990, pp77-9
7. Anon., "Drug consumption in the elderly in Italy", *Scrip*, No 1721/2, 27/29 May 1992, p4
8. Schneider, J.K., Mion, L.C., and Frengley, J.D., "Adverse drug reactions in an elderly outpatient population", *American Journal of Hospital Pharmacy*, Vol 49, Jan 1992, pp90-6
9. Anon., "Problems of aging overestimated?", *Scrip*, No 1655, 27 Sep 1991, pp4-5
10. Lexchin, J., "Adverse drug reactions", *Canadian Family Physician*, Vol 37, Jan 1991, pp109-18
11. Anon., "Drugs and the elderly - US debate continues", *Scrip*, No 1407, 28 Apr 1989, p18
12. Advertisement in the *American Journal of Medicine*, Vol 91, No 2, Aug 1991, ppA30-A32
13. Dukes, M.N.G. and Beeley, L., (eds), *Side Effects of Drugs Annual 14*, Amsterdam, Elsevier, 1990, p86
14. Anon., "Prescriptions for profit", transcript of a television documentary broadcast on the *Frontline* programme on 28 Mar 1989, Boston, WGBH Transcripts, p29
15. Anon., "Drug effects in the elderly", *WHO Drug Information*, Vol 5, No 2, 1991, p61
16. Bird, op cit
17. Laurence, D.R. and Bennett, P.N., *Clinical Pharmacology*, Edinburgh, Churchill Livingstone, (6th edn), 1987, pp140-2
18. Parish, P., *Medicines: a guide for everybody*, London, Penguin (6th edn, revised), 1989, p32
19. BMA and the Royal Pharmaceutical Society of Great Britain, *British National Formulary*, London, BMA and The Pharmaceutical Press, No 23, Mar 1992, p14
20. Ibid
21. Williamson, J., "Introduction", *British Medical Bulletin*, Vol 46, No 1, 1990, pp1-8
22. Wolfe, S.M., Fugate, L., et al, *Worst Pills Best Pills*, Washington, Public Citizen Health Research Group, 1988, pp69-70
23. Potter, J.F. and Haigh, R.A., "Benefits of anti-hypertensive therapy in the elderly", *British Medical Bulletin*, Vol 46, No 1, 1990, pp77-93
24. Laurence and Bennett, op cit, p142
25. Swift, C.G., "Prescribing for the elderly", in: Feely, J. (ed.), *New Drugs*, London, British Medical Journal, 1991, pp65-73
26. Collier, J., *The Health Conspiracy*, London, Century Hutchinson, 1989, p15
27. Wolfe, et al, op cit, p8
28. Hart, R.P., Colenda, C.C. and Hamer, R.M., "Effects of buspirone and alprazolam on the cognitive performance of normal elderly subjects", *American Journal of Psychiatry*, Vol 148, No 1, Jan 1991, pp73-7
29. Parish, op cit, p32
30. Cumming, R.G., Miller, J.P., et al, "Medications and multiple falls in elderly people: the St Louis OASIS Study", *Age and Ageing*, Vol 20, 1991, pp455-61
31. Nuki, G. and Pullar, T., "Non-steroidal analgesic and anti-inflammatory agents", in: Feely, op cit, pp330-44
32. Bird, H.A., "Drugs and the elderly", *Annals of the Rheumatic Diseases*, Vol 49, 1990, pp1021-2
33. Dumas, C. and Cusack, B.J., "Salicylate intoxication in the elderly: recognition and recommendations on how to prevent it", *Drugs & Aging*, Vol 2, No 1, 1992, pp20-34
34. Nuki and Pullar, op cit
35. Sirgo, M.A. and Norris, S.; "Ceftazidime in the Elderly: Appropriateness of twice-daily dosing", *DICP, The Annals of Pharmacotherapy*, Vol 25, Mar 1991, pp284-8
36. Yoshikawa, T.T., "Antimicrobial therapy for the elderly patient", *Journal of the American Geriatric Society*, Vol 38, No 12, Dec 1990, pp1353-72
37. Sirgo and Norris, op cit
38. Sanderson, P., "Antibiotics and the elderly", *The Practitioner*, Vol 234, Dec 1990, pp1064-6
39. Anon., "Australian ADRs", *Scrip*, No 1500, 28 Mar 1990, p30
40. Yoshikawa, op cit
41. Moran, J., *Alzheimer's Disease: New Therapies and the World Market*, London, Financial Times Management Reports, 1991
42. Gilman, A.G., Rall, T.W., Nies, A.S., and Taylor, P., *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, New York, Pergamon Press, (8th edn) 1990, p781
43. BMA and the Royal Pharmaceutical Society of Great Britain, op cit, p92
44. Mansfield, P.R., "Classifying improvements to drug marketing and justifications for claims of efficacy", *International Journal of Risk & Safety in Medicine*, Vol 2, 1991, pp171-84
45. Lowenthal and Nadeau, op cit
46. Ibid
47. Williamson, op cit
48. Laurence and Bennett, op cit, p142
49. Parish, op cit, p32
50. BMA and the Royal Pharmaceutical Society of Great Britain, op cit, p14

Chetley, A. *Problem Drugs*, Amsterdam, Health Action International, 1993

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2A. Antidiarrhoeals

Dying for lack of a drink

A 9-month old infant was suffering from vomiting and diarrhoea. His mother was advised by telephone by a hospital paediatrician to purchase a commercial brand of oral rehydration solution and was given instructions on how to use the product correctly. She was also advised to call back if the child's symptoms worsened or if he was unable to drink enough of the fluid. The mother went to her local pharmacy, but did not have enough money to buy the solution. The following day, the child's vomiting continued and the diarrhoea increased. The mother continued to feed the child with an infant formula and with solid foods, but the child's condition deteriorated. The next morning, the mother took the child to the hospital emergency department. Despite three days of intensive care in the hospital, the child died. This death occurred in Boston, USA.[1]

Four million children a year die from diarrhoeal diseases.[2] A simple, highly effective therapy – oral rehydration therapy (ORT) – plus continued feeding can prevent at least half of those deaths,[3] at a cost of little more than 50 cents a child.[4] Instead, hundreds of millions of dollars are wasted on so-called antidiarrhoeal medicines that are at best ineffective and at worst dangerous. According to the World Health Organization (WHO), "this expenditure cannot be justified".[5]

Diarrhoea is one of the leading causes of illness and death in the developing world,[6] where poverty, poor sanitation, a lack of clean water and increased exposure to infections are prevalent. It is also a serious problem in the industrialised world. Studies in Western Europe and North America have shown that diarrhoea is the second most common reason for children to be hospitalised.[7] In the USA, for example, after a 10-year survey of national mortality data, the Centers for Disease Control in Atlanta concluded in 1988 that "diarrhoeal deaths constitute an important and preventable fraction of postneonatal mortality in American children" and represent about 10% of preventable childhood deaths.[8]

There are many causes of diarrhoea.[9] Worldwide, viruses account for approximately 50% of all cases of diarrhoea and are responsible for approximately 40% of all deaths that are attributed to diarrhoea.[10] The rotavirus is the most frequent cause of diarrhoea in infants and children under two years of age.[11] Viral infection is particularly likely in industrialised countries, whereas in developing countries there can be a greater incidence of diarrhoea caused by bacteria such as *Shigella* or *Escherichia coli* (*E. coli*) or parasites and various amoebae.[12] Nonetheless, a two-year study of children with acute diarrhoea in five hospitals in China, India, Mexico, Myanmar (formerly Burma) and Pakistan found that rotavirus was the most frequent cause of diarrhoea during the first year of life.[13] Diarrhoea can also occur as a result of some drug therapy; for example, nearly all antibiotics can induce diarrhoea.[14] The incidence of diarrhoea is higher amongst infants who are bottle fed rather than breastfed.[15] Stress, tension, and change of diet can also bring about episodes of diarrhoea. Diarrhoea

Table 2A-1
Drugs which commonly cause diarrhoea

Antimicrobials (sulphonamides, tetracyclines, most broad-spectrum antibiotics)
Cholinergic agonists and cholinesterase inhibitors
Osmotic laxatives (sorbitol, saline cathartics)
Prokinetic agents (metoclopramide, domperidone)
Prostaglandins
Stimulant laxatives

Source: Adapted from Gilman, A.G., Rall, T.W., Nies, A.S., and Taylor, P., *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, New York, Pergamon Press, (8th edn) 1990, p924

accompanies between 20 and 60% of cases of measles, and within six months of having had measles, 10 to 20% of children will have a diarrhoea attack which they would otherwise not have had.[16]

Diarrhoea is usually described as being acute, lasting from a few hours to a few days, or persistent, lasting two weeks or more or involving regularly recurring episodes. Most diarrhoea is acute and self-limiting – that is, it goes away by itself. Diarrhoea is not a *disease*, but a *symptom*.[17] Put simply, diarrhoea is the body's way of removing foreign toxins, bacteria or other materials which upset the gut. It is a natural protective mechanism. The danger of diarrhoea, and the most frequent cause of death, particularly in infants and young children, is the accompanying dehydration due to the loss of large amounts of water and salts (electrolytes).[18] "A great many infants suffering from diarrhoea do not die from the disease but from mismanagement – and the principal cause of death is dehydration."[19]

Oral rehydration therapy (ORT): "potentially the most important medical breakthrough this century".
(*The Lancet*, 5 Aug 1978. p300)

Oral rehydration therapy (ORT)

Preventing diarrhoea from occurring in the first place is the best long-term solution (see box on right). However, if diarrhoea occurs, the prevention and treatment of dehydration should be the first priority.[20] ORT is effective in preventing and treating almost all cases of dehydration from acute watery (non-bloody) diarrhoea, including cholera.[21]

Studies from around the world demonstrate the remarkable ability of ORT to reduce the number of deaths caused by diarrhoea. ORT contributed to a 50% reduction in the number of children admitted to hospital and the number of children dying as a result of diarrhoea-related dehydration in a major hospital in Natal, South Africa, between 1986 and 1990.[22] In the first two years following training of paediatric staff in the use of ORT and the establishment of an oral rehydration unit at the Kamuzu Central Hospital in Lilongwe, Malawi, there was a 50% decrease in the number of children admitted to the paediatric ward with the diagnosis of diarrhoeal diseases and a 39% decrease in the number of paediatric deaths associated with diarrhoeal diseases. Over the same period, there was a 32% decrease in recurrent hospital costs attributable to paediatric diarrhoeal diseases.[23] In Mexico City, the introduction of an oral rehydration unit at one of the main children's hospitals led to a 25% decrease in the number of children under five years of age admitted with diarrhoea between 1983 and 1986.[24] In a major hospital in the capital of Lesotho, admissions of children suffering from diarrhoea declined from 23% of all paediatric admissions to 13% after the opening of an oral rehydration therapy unit.[25] In Egypt, a national programme to control diarrhoea, making extensive use of oral rehydration therapy, has contributed to a decline in infant mortality of at least 36% between 1982 and 1987.[26]

Preventing diarrhoea

Poverty and lack of basic services may make it difficult for families to prevent diarrhoea. However, there are effective ways of preventing diarrhoea which cost little or no money.

The most cost-effective preventive interventions are: promotion of exclusive breastfeeding; improved weaning practices; use of plenty of clean water; washing hands; use of latrines; proper disposal of excrement, particularly that of infants and children; and measles immunisation.

- Give breast milk alone for the first four to six months of a baby's life. Breast milk helps protect babies against diarrhoea and other illnesses.
- At the age of four to six months, introduce clean, nutritious, well-mashed, semi-solid foods and continue to breastfeed.
- Use the cleanest water available for drinking. Water from wells, springs or rivers should be brought to the boil before use. Keep the water in clean containers and keep hands out of the containers. Use a clean pot or jar to take water from the containers.
- If possible, food should be thoroughly cooked, and prepared just before eating. It should not be left standing, or it will collect germs. If food is to be used more than two hours after preparation, heat it again.
- Always use latrines to dispose of human excrement, particularly that of children (or bury children's excrement immediately).
- Wash hands with soap and water immediately after using the latrine, after cleaning a child, before preparing or eating food, and before feeding a child.
- Vaccinate children against measles because measles frequently results in severe diarrhoea. This helps to prevent one important cause of diarrhoea, even though a general vaccine against diarrhoea is not available.

Sources: UNICEF, WHO and UNESCO, *Facts for Life: A Communication Challenge*, New York, UNICEF, 1989, pp47 8, Feachem, R , "Preventing diarrhoea: what are the policy options?", *Health Policy and Planning*, Vol 1, No 2, 1986, pp109-17

The wrong kind of medicine

Despite the unprecedented effectiveness of ORT, its use is not yet as widespread as it could be. Why? One factor is unquestionably the widespread availability, the continuing dispensing and prescription, and aggressive promotion of a large variety of "antidiarrhoeal" drugs.

In India, for example, a survey of 15,000 doctors found that two-thirds claimed to use ORT in their

practice; however, 37% of the doctors claimed that antidiarrhoeal preparations were "absolutely essential" in all cases of diarrhoea, and another 55% said they were "sometimes essential". Forty percent of the doctors said they used antibiotics to treat diarrhoea, although most claimed to use them only in selected cases. Rolf Carriere of UNICEF commented that "this use of antidiarrhoeals by nearly all respondents demonstrates the extent of the problem, for these drugs generally divert attention from oral rehydration and are also too expensive for most families."[27] A smaller survey at one of the leading teaching hospitals in India found that 92% of children admitted with mild or moderate dehydration received an antidiarrhoeal preparation, often in combination with an antibiotic. Dr C. R. Soman, a Professor of Nutrition in India, points out that such practices are not surprising given that one of the most popular Indian textbooks, *Pharmacology and Therapeutics*, devoted nearly three pages to discussing the various drugs to be used in the symptomatic treatment of diarrhoea, but did not mention oral rehydration in the chapter on diarrhoea.[28]

A child with diarrhoea is like a pot with a large hole. Treat the child by filling up the pot faster than the water flows out. Prevent diarrhoea by making the pot strong. Give the child plenty of food. If the child has diarrhoea again, start treatment immediately. This will prevent dehydration.

Dr Mira Shiva and Aspi B. Mistry, *A Taste of Tears*, New Delhi: Voluntary Health Association of India, 1983

National studies carried out in Peru in 1984 and 1986 found that the use of antidiarrhoeal medicines was increasing. In 1984, 49% of children under one year of age with diarrhoea and 53% of children from one to five years of age were receiving antidiarrhoeal products; while in 1986, 62% of children under the age of five with diarrhoea were receiving antidiarrhoeal products. These national surveys did not indicate whether the use of these products was necessary. However, a smaller scale study carried out in the community of Canto Grande in Lima from 1984 to 1989 clearly indicates that a large proportion of antidiarrhoeal use is unnecessary. The use of drugs to treat diarrhoea in children under three years of age increased from 19% of cases to nearly 60% during the period of the study. While the appropriate use of medication (usually antibiotics for *Shigella* dysentery) increased from 3% to 32% of diarrhoea episodes, unfortunately the misuse or inappropriate use of drugs also increased from 16% to 28% of cases over the period (see Table 2A-2).[29] In the year from June 1988 to June 1989, sales of inappropriate antidiarrhoeal products in Peru amounted to US $2,156,000. To this, an estimated $290,000 could be added to include the proportion of sales of the antibiotic, chloramphenicol, which was used inappropriately for diarrhoea.[30]

In a leading children's hospital in Mexico City, children admitted with diarrhoea were treated with at

Oral rehydration salts

While there is no debate about the wisdom of replacing the fluids lost by children with diarrhoea, there is some discussion about the best way to do this. WHO and UNICEF have developed a packet of oral rehydration salts (ORS) which combines salt, sugar, baking soda and potassium and which, when mixed with water, provides a balanced solution which helps to replace the lost fluids and minerals and helps to prevent further losses.[1]
One of the difficulties with ORS packets is that they tend to over-medicalise the treatment of dehydration, create dependence and, even though they are inexpensive, do nonetheless cost some money to buy. Public health specialist, David Werner, suggests that to teach mothers to prepare appropriate drinks at home is a more "sustainable, empowering approach" which encourages self-reliance.[2]

A home-made cereal-based drink which makes use of sorghum, rice, wheat, millet, maize or potato – staple foods in developing countries – is one way of increasing children's fluid intake. Research now shows that cereal-based drinks also help to deal with the diarrhoea by reducing the stool output, something which ORS does not do.[3]

Sources:
1. WHO, *The treatment and prevention of acute diarrhoea. Practical guidelines*, Geneva, WHO, (2nd edn) 1989, p18
2. Werner, D., "Egypt: another approaching storm on the desert", *Newsletter from the Sierra Madre*, No 24, June 1991, p5
3. Molla, A.M., Molla, A., Nath, S.K., et al, "Food based oral rehydration salt solution for acute childhood diarrhoea", *Lancet*, 19 Aug 1989, pp429-31
Carpenter, C.C.J., Greenough, W.B., Pierce, N.F., "Oral-rehydration therapy – the role of polymeric substrates", *New England Journal of Medicine*, Vol 319, No 20, 17 Nov 1988, pp1346-8
WHO, "Research findings support use of rice based ORS", *Essential Drugs Monitor*, No 10, 1990, p18
Sack, D.A., "Use of oral rehydration in acute watery diarrhoea: a practical guide", *Drugs*, 41:4, 1991, pp566-73

Table 2A-2
Percentage of episodes of diarrhoea in children under three years of age treated with appropriate or inappropriate medicines in Canto Grande, Lima, Peru (1984-1989)

	1984	1985	1986	1987	1988	1989
Number of episodes	1521	2324	2424	1854	6327	5892
Total percentage treated with drugs	18.7	28.6	38.1	34.2	33.2	59.8
Percentage of episodes where drug therapy was probably indicated	3.2	7.0	10.2	9.4	12.8	32.1
Percentage of episodes where drug therapy was not indicated or was not necessary	15.5	21.6	27.9	24.8	20.4	27.7

Source: Cruz, H., Paredes, P., and Haak, H., *Medicamentos Inapropiados en Diarrea: La magnitud del problema*, Lima, Peru, Pan-American Health Organization, Nov 1989, p25

least one antibiotic in about half the cases in 1983 and in 1986. Researchers pointed out that this use of antibiotics was "difficult to justify"; in 1986, for example, there were no cholera cases and only one of the patients had been diagnosed as infected with *Shigella* dysentery. The hospital could have saved an estimated two million pesos (US $2,000) had those patients not received antibiotics.[31]

A survey in northern Iran found that 90 out of 100 children admitted to hospital with diarrhoea had previously been treated unsuccessfully with a variety of drugs, including antibiotics and anti-motility agents.[32]

A study of the 902 diarrhoeal cases dealt with by 58 physicians in western Sicily in a 12-month period during 1984-85 found that although oral rehydration therapy was widely known by both general practitioners and paediatricians, 65% of all cases were treated with antibiotics and 8% of cases were treated with anti-motility drugs. Only 9% of cases were treated with ORT alone.[33]

A survey of 75 pharmacies in Bangladesh, Sri Lanka and the Yemen Arab Republic (25 pharmacies in each country) during 1984 and 1985 found that only 21% advised oral rehydration or consultation with a health worker for diarrhoea. Instead, most pharmacies were dispensing combination antibiotics. In Yemen, for example, over 40% of the treatments given out contained neomycin.[34]

A survey of 13 pharmacies in Kenya in 1989 found that oral rehydration was not recommended in any of them as the first line treatment for diarrhoea for a two-year old child. In one pharmacy, oral rehydration was recommended as a second line treatment. Seven of the pharmacies recommended products containing an antibiotic, including four which contained neomycin. Ten of the products recommended contained kaolin and pectin and one was diphenoxylate syrup. Only five of the pharmacies even stocked oral rehydration solution.[35]

A survey of 30 pharmacies in one city in England in 1989 found a large proportion of pharmacists recommending inappropriate therapy. The survey took the form of visits to 10 pharmacies chosen at random where a female investigator entered posing as a mother who had a child with diarrhoea, and, in 20 other pharmacies, interviews with pharmacists who were also asked to complete a questionnaire. Half the pharmacists interviewed and nearly three quarters in the "staged" visits recommended the use of an antidiarrhoeal product rather than oral rehydration. Equally disturbing was the response of the 20 pharmacists to questions about feeding practices for children with diarrhoea: half suggested stopping all milk and half suggested stopping all food, while two-thirds believed it was necessary to stop breastfeeding during diarrhoea.[36]

A survey of 63 pharmacies in Khartoum, Sudan, in 1988 found that 62% of pharmacists recommended the use of an antibiotic for the treatment of a one-year old child with acute diarrhoea. Only three pharmacies (5%) recommended the use of oral rehydration.[37]

How effective are they?

WHO has no doubt about the role of antidiarrhoeal products: "There are no drugs available at present that will safely and effectively stop diarrhoea."[38] "Most medicines for diarrhoea are either useless or harmful."[39]

Many developing countries have governmental programmes to control diarrhoeal diseases. These programmes rely primarily on ORT for treatment and a few antimicrobials for specific conditions (as listed in table 2A-4). Antidiarrhoeals are not considered to be useful and their availability on the market can interfere with a programme's success.[40]

The major types of drugs used (often incorrectly) in the treatment of diarrhoea are: *anti-motility drugs; antimicrobial agents; adsorbents; hydroxyquinolines; intestinal bacteria supplements.*

Table 2A-3
Antidiarrhoeals containing antimicrobials (1986 and 1988-89)[1]

Country/ region	Total anti-diarrhoeals		Total containing antimicrobials				Total containing neomycin			
	1986	1988-9	1986		1988-9		1986		1988-9	
	No.	No.	No.	%	No.	%	No.	%	No.	%
Africa	29	22	16	55.2	3	13.6	7	24.1		
Caribbean	18	18	10	55.6	5	27.8	5	27.8	2	11.1
Hong Kong	26	21	7	26.9	6	28.6				
Indonesia[2]	53	62	33	62.3	32	51.6	8	15.1	8	12.9
India	63	59	51	81.0	47	79.7	7	11.1	4	6.8
Middle East	41	23	22	53.7	6	26.1	7	17.1		
Malaysia & Singapore	29	19	13	44.8	1	5.3	6	20.7		
Mexico[1]	72	69	46	63.9	44	63.8	5	6.9	5	7.2
Philippines	62	46	38	61.3	25	54.3				
Pakistan	56	53	36	64.3	17	32.1	6	10.7		
Thailand	57	72	29	50.9	38	52.8	10	17.5	11	15.3
Totals	506	464	301	59.5	224	48.3	61	12.1	30	6.5

Notes:
1. Data from Mexico are from 1987
2. In October 1991, the government of Indonesia deregistered 94 antidiarrhoeal products, including many which contained antibiotics. For further information, see: Anon., "Daftar 285 Obat Yang Ditarik Dari Peredaran" (List of 285 drugs which are withdrawn from circulation), *Suara Pembaruan*, 29 Oct 1991.

Sources: *MIMS Africa* (Nov 86 and Jul 89), *MIMS Caribbean* (Nov 86 and May 89), *HKIMS* (Hong Kong, Aug 86 and Dec 88), *IIMS* (Indonesia, June 86 and Oct 88), *MIMS India* (June 86 and Feb 88), *MIMS Middle East* (Oct 86 and Aug 89), *DIMS* (Malaysia & Singapore, June 86 and Oct 88), *Diccionario de Especialidades Farmaceuticas* (Mexico, 1986 and 1987), *PIMS* (Philippines, Aug 86 and Dec 88), *QIMP* (Pakistan, Mar-Sept 86 and Sep 88-Feb 89) and *TIMS* (Thailand, July 86 and Nov 88)

Anti-motility drugs

Anti-motility drugs operate on the premise that the symptom (diarrhoea) must be stopped. Basically, these drugs slow down the functions of the gut. WHO says these products have no role in the treatment of diarrhoea in children[41] and that they "may be harmful, especially for children below 5 years of age. They... delay the elimination from the body of the organisms that cause the diarrhoea, and may prolong the illness. They can be dangerous, and even fatal, if used incorrectly in infants."[42]

Two important products which fall into this category are loperamide (Imodium) manufactured by Janssen (Johnson & Johnson) and diphenoxylate (Lomotil with atropine) manufactured by Searle.

[See sections on *Loperamide* and *Diphenoxylate* for further details.]

Antimicrobial agents

Nearly half the 464 antidiarrhoeal preparations on sale in 11 regions of the world during 1988-9 contained an antimicrobial, as Table 2A-3 shows. More than 160 companies are involved in this trade – ranging from small, national ventures trading only in their own country, up to the large transnationals such as Abbott, Boehringer Mannheim, Boots, Bristol-Myers, Dainippon, Dumex, Fisons, Glaxo, Grünenthal, Hoechst, Merck Sharp & Dohme, May & Baker, Nattermann, Parke-Davis/Warner Lambert, Pfizer, Rorer, Searle, SmithKline, Sterling Winthrop, Upjohn, Carter-Wallace, and Wyeth.[43]

For over 20 years, antimicrobials were used as the main treatment in diarrhoea. Now, however, authoritative opinion is against their use in all but a few specific infections. This is because antimicrobial drugs may:

- alter the normal bacterial content of the gut leading to possible fungal infections and overgrowth of resistant bacteria;
- prolong the period when the patient with an infection can pass on the disease as a carrier;
- increase the risk of relapse;
- interfere with subsequent bacteriological diagnosis.[44]

According to WHO, "Antibiotics are not effective against most organisms that cause diarrhoea. They rarely help and can make some people sicker in the long term. Their indiscriminate use may increase the resistance of some disease-causing organisms to antibiotics. In addition, antibiotics are costly, so money is wasted. Therefore, antibiotics should not be used routinely."[45] (See Table 2A-4 for advice on which antibiotics to use for dysentery and cholera.)

Other experts agree. "Antibiotics have a limited role in the management of diarrhoea."[46] In most cases, "Less than one-tenth of patients with acute diarrhoea can be treated successfully with antimicrobial drugs."[47]

Table 2A-4
Antimicrobials recommended by WHO for the treatment of specific causes of diarrhoea in children

Cause	Antibiotic(s) of choice[1]	Alternatives[1]
Cholera[2,3]	*Tetracycline* 12.5 mg/kg body weight 4 times a day x 3 days	*Furazolidone* 1.25 mg/kg body weight 4 times a day x 3 days or *Trimethoprim (TMP)-sulfamethoxazole (SMX)*[4] TMP 5 mg/kg body weight and SMX 25 mg/kg body weight twice a day x 3 days
Shigella dysentery[2]	*Trimethoprim (TMP)-sulfamethoxazole (SMX)* TMP 5 mg/kg body weight and SMX 25 mg/kg body weight twice a day x 5 days	*Nalidixic acid* 15 mg/kg body weight 4 times a day x 5 days or *Ampicillin* 25 mg/kg body weight 4 times a day x 5 days
Amoebiasis	*Metronidazole* 10 mg/kg body weight 3 times a day x 5 days (10 days for severe disease)	In very severe cases: *Dehydroemetine hydrochloride* by deep, intramuscular injection, 1-1.5 mg/kg body weight daily (maximum 90 mg) for up to 5 days, depending on response
Giardiasis	*Metronidazole*[5] 5 mg/kg body weight 3 times a day x 5 days	*Quinacrine* 2.5 mg/kg body weight 3 times a day x 5 days

Notes:
1. All doses shown are for oral administration unless otherwise indicated. If drugs are not available in liquid form for use in young children, it may be necessary to approximate the doses given in this table.
2. The choice of antibiotic will depend on the frequency of resistance to antibiotics in the area.
3. Antibiotic therapy is not essential for successful treatment, but it shortens the duration of illness and the period of excretion of organisms in severe cases.
4. Other alternatives are erythromycin and chloramphenicol.
5. Tinidazole and ornidazole can also be used in accordance with the manufacturers' recommendations.

Source: WHO, *The rational use of drugs in the management of acute diarrhoea in children*, Geneva, WHO, 1990, p3

All the antibiotics currently used in the treatment of diarrhoea have side effects that should be carefully monitored. The use of antibiotics prophylactically (in an attempt to prevent diarrhoea) can contribute to the widespread emergence and spread of antimicrobial resistance. The costs of such an approach are likely to be high and there may be no long-term benefits. The available evidence therefore suggests that such an approach is not a cost-effective intervention for national diarrhoeal disease control programmes.[48]

At least $150 million a year is wasted on antidiarrhoeal drugs which contain antimicrobial agents.[49]

[See also the sections on *Antidiarrhoeals containing antibiotics* and *Antibiotics*.]

Hydroxyquinolines

Hydroxyquinolines were discovered to have some effect in amoebic dysentery, but their use has broadened out to include most types of diarrhoea. The best-known drug in this category is Entero-Vioform (clioquinol) which was formerly manufactured by Ciba-Geigy, but was withdrawn from the world market in 1985.

According to the American Medical Association,

> "Clioquinol... and iodoquinol... have been used in the prophylaxis of travellers' diarrhoea but proof of their efficacy is lacking.... Since amoebae cause only a small percentage of the diarrhoea encountered while travelling, the indiscriminate use of such potentially toxic agents is unjustified. Clioquinol is no longer available for systemic use in the United States."[50]

All of the hydroxyquinolines carry a high risk of adverse effects and most experts agree that their use should be avoided because they are both ineffective and dangerous.[51]

[See also the section on *Hydroxyquinolines*.]

Adsorbents

Adsorbents are supposed to attach themselves to toxins and various infective agents (as well as to some therapeutic agents) and in theory help to detoxify the gut. The main adsorbents used in antidiarrhoeal drugs are *kaolin* (usually with *pectin* – a stabilising agent), *activated charcoal* and *attapulgite*. WHO says these products "are not useful for the treatment of acute diarrhoea".[52]

The American Medical Association describes the use of mixtures containing opiates or poorly absorbed antibacterial agents with adsorbents such as kaolin and pectin and antispasmodic agents as "unwarranted." It

Table 2A-5
Comparison of antidiarrhoeal drugs in selected prescribing guides

Source	Total no. of antidiarrhoeal products	No. of products with ineffective contents				No. of products with high risk			Total: ineffective and/or high risk	
		Ads	Flo	Lop	Opi	Neo	Cli	Nra	No.	%
India (MIMS)										
Jun 85:	47	21		7	10	7	6	24	39	(82.9%)
Feb 88:	62	23		11	8	4	8	30	58	(93.5%)
Indonesia (IIMS)										
Feb 85:	49	22	3	6	3	6	18	22	46	(93.8%)
Oct 88:	62*	21	3	18	13	8	19	25	62	(100%)
Middle East (MIMS)										
Apr 85:	37	21	1	2	7	9	8	17	33	(89.1%)
Dec 90:	21	4		6	3			6	16	(76.2%)
Africa (MIMS)										
May 85:	28	18	1	1	5	9	7	12	25	(89.2%)
Jan 91:	16	4		4	2			3	12	(75.0%)
Caribbean (MIMS)										
May 85:	19	12		2	5	6	4	7	18	(94.7%)
Jan 91:	14	6		5	2	2		2	13	(92.9%)

Key: Ads = Adsorbents; Flo = Intestinal bacteria supplements; Lop = loperamide; Opi = other opiates; Neo = Neomycin; Cli = clioquinol and other hydroxyquinolines; Nra = other non-recommended antibacterials

Notes:
The total in the final column is less than the sum of the individual items, due to some drugs being irrational combinations of two or more chemicals.
*In October 1991, the government of Indonesia deregistered 94 antidiarrhoeal products. For further information, see: Anon., "Daftar 285 Obat Yang Ditarik Dari Peredaran" (List of 285 drugs which are withdrawn from circulation), *Suara Pembaruan*, 29 Oct 1991

notes that the patient is subjected to the combined adverse effects of the individual ingredients and the added expense of all of these agents. Among the preparations it cites are: Corrective Mixture (Beecham), Donnagel and Donnagel PG (Robins), Kaolin with Pectin (various), Kaopectate and Kaopectate Concentrate (Upjohn), Parepectolin (Rorer), Polymagma (Wyeth).[53]

In Pakistan in 1991, Dr Tariq Bhutta, a paediatrician at the Nishtar Hospital in Multan, said that he was "not very optimistic" about being able to remove some of the useless kaolin and pectin mixtures from the market. He had been in contact with both Abbott and Wyeth asking them to withdraw their respective products (Katlin and Strepomegma) in the light of the WHO recommendation. Both companies responded that they had no intention of doing so as the products are permitted by many governments.[54]

Intestinal bacteria supplements

The theory behind the use of lactobacillus and other intestinal bacteria supplements is that the diarrhoea causes the loss of normal intestinal bacteria, and that replacing these "friendly" bacteria will help. However, as the *Martindale* guide to medicines points out, "evidence to support this use is limited".[55]

Missing the target

The firm conclusion is that the vast majority of antidiarrhoeal drugs on the market worldwide are – at best – unnecessary and, at worst, ineffective and sometimes dangerous. A survey in 1980 found that 85% of antidiarrhoeals listed in the MIMS prescribing guide for Africa were "undesirable"; 80% in the Caribbean; 82% in the Middle East; 73% in Philippines; 74% in Malaysia and Singapore; and 79% in Indonesia.[56] Sadly, the situation has not improved much over the years, as Table 2A-5 indicates.

A survey carried out in 1990 in 12 countries in Latin America – Argentina, Bolivia, Brazil, Chile, Colombia, Costa Rica, Ecuador, Guatemala, Mexico, Peru, Uruguay and Venezuela – found a total of 351 antidiarrhoeal preparations marketed. The vast majority (78%) of these were combination products containing from two to nine active ingredients, while 63% of the products contained one or more antibiotics. Loperamide was present in 15% of the products, and 12% contained clioquinol or another hydroxyquinoline.[57]

It is difficult to reconcile the fact that over 80% of the products on the market have no efficacy in the treatment of acute diarrhoea with the fact that four million children are dying each year from diarrhoea.

It is time that waste was stopped.

Recommendations for action

1. Governments and health workers should develop rational management policies for the control of diarrhoeal diseases. These should include the provision of clear and independent information and education for patients and consumers about the appropriate treatment of diarrhoea.
2. All products labelled as antidiarrhoeals and containing antimicrobial agents should be withdrawn from the market.
3. The use of antimicrobials in treating diarrhoea should be limited to those drugs and specific indications set out by WHO (see Table 2A-4).
4. All paediatric products containing an anti-motility drug should be withdrawn from the market.
5. Antidiarrhoeal preparations with no proven efficacy, such as adsorbents and intestinal bacteria supplements, should be removed from the market.
6. All antidiarrhoeal preparations should carry a large, clear message on the package, and in all information and advertising material, to the effect that ORT is the main therapy in the management of diarrhoea.

Notes and references:

1. Meyers, A., Siegel, B., and Vinci, R., "Economic barriers to the use of Oral Rehydration Therapy: a case report", *Journal of the American Medical Association*, Vol 265, No 13, 3 Apr 1991, p1724
2. WHO, *The rational use of drugs in the management of acute diarrhoea in children*, Geneva, WHO, 1990, p1
   WHO, *A manual for the treatment of diarrhoea*, (WHO/CDD/SER/80.2 Rev.2 1990), Geneva, WHO, 1990, p1
3. WHO/UNICEF, *Lessons learned: management of childhood diarrhoea*, paper prepared for Joint UNICEF/WHO CDD Strategy Meeting, 15 Apr 1991, p1
4. UNICEF, *The State of the World's Children 1991*, Oxford and New York, Oxford University Press, 1990, p12
   Anon., "$1 b wasted on useless drugs, says WHO", *Scrip*, No 1633, 12 Jul 1991, p22
5. WHO, "Rational management of diarrhoea in children", *Essential Drugs Monitor*, No 11, 1991, p10
6. Snyder, J.D., "Use and misuse of oral therapy for diarrhea: comparison of US practices with American Academy of Pediatrics recommendations", *Pediatrics*, Vol 87, No 1, Jan 1991, p28
   Edmundson, S.A., Edmundson, W.C., "Acute diarrhoeal disease in India and Indonesia", *Social Sciences and Medicine*, Vol 29, No 8, 1989, pp991-7
   Fujita, K., Kaku, M., Yanagase, Y., et al, "Physicochemical characteristics and flora of diarrhoeal and recovery faeces in children with acute gastroenteritis in Kenya", *Annals of Tropical Paediatrics*, Vol 10, 1990, pp339-45
   Mata, L., "How harmful is diarrhoea?", *World Health*, Apr 1986, pp5-7
7. Balistreri, W.F., "Oral rehydration in acute infantile diarrhea", *American Journal of Medicine*, Vol 88, No 6A, 20 Jun 1990, pp30S-33S
   Conlon, C.P. and Peto, T.E.A., "Infectious diarrhoea", *International Journal of Colorectal Disease*, Vol 5, 1990, pp236-40
   Carpenter, C.C.J., Greenough, W.B., and Pierce, N.F., "Oral rehydration therapy – the role of polymeric substrates", *New England Journal of Medicine*, Vol 319, No 20, 17 Nov 1988, pp1346-8
   Fedorak, R.N., Field, M., "Antidiarrheal therapy: prospects for new agents", *Digestive Diseases and Sciences*, Vol 32, No 2, Feb 1987, pp195-205
   Radetsky, M., "Laboratory evaluation of acute diarrhea", *Pediatric Infectious Disease*, Vol 5, No 2, Mar 1986, pp230-8
   Snyder, J.D., op cit
   Glass, R.I., Lew, J.F., Gangarosa, R.E., et al, "Estimates of morbidity and mortality rates for diarrheal diseases in American children", *Journal of Pediatrics*, Vol 118, No 4, Apr 1991, pp27-33
   Meyers, A., Siegel, B., and Vinci, R., op cit
8. Ho, M.S., Glass, R.I., Pinsky, P.F., et al, "Diarrheal deaths in American children: are they preventable?", *Journal of the American Medical Association*, Vol 260, 1988, pp3281-4
9. AMA, *Drug Evaluations*, Philadelphia, W.B. Saunders Co., (6th edn) 1986, p959
10. Soriano-Brucher, H., Avendano, P., O'Ryan, M., et al, "Bismuth subsalicylate in the treatment of acute diarrhea in children: a clinical study", *Pediatrics*, Vol 87, No 1, Jan 1991, pp18-27
    Henry, F.J., Bartholomew, R.K., "Epidemiology and transmission of rotavirus infections and diarrhoea, in St. Lucia, West Indies", *West Indies Medical Journal*, Vol 39, 1990, pp205-12
    Ansari, S.A., Springthorpe, S., and Sattar, S.A., "Survival and vehicular spread of human rotaviruses: possible relation to seasonality of outbreaks", *Reviews of Infectious Diseases*, 13, 1991, pp448-61
11. Maldonado, Y.A. and Yolken, R.H., "Rotavirus", *Balliere's Clinical Gastroenterology*, Vol 4, No 3, Sep 1990, pp609-25
12. Po, A.L.W., *Non-Prescription Drugs*, Oxford, Blackwell Scientific, (2nd edn) 1990, pp210-11
    Cohen, M.B., "Etiology and mechanisms of acute infectious diarrhea in infants in the United States", *Journal of Pediatrics*, Vol 118, No 4, Apr 1991, pp34-39
    Fujita, K., Kaku, M., Yanagase, Y., et al, op cit
    Nakano, T., Binka, F.N., Afari, E.A., et al, "Survey of enteropathogenic agents in children with and without diarrhoea in Ghana", *Journal of Tropical Medicine and Hygiene*, Vol 93, 1990, pp408-12
    Gorbach, S.L., "Bacterial diarrhoea and its treatment", *Lancet*, 12 Dec 1987, pp1378-1382
13. Huilan, S., Lu, G.Z., Mathan, M.M., et al, "Etiology of acute diarrhoea among children in developing countries: a multicentre study in five countries", *Bulletin of the World Health Organization*, Vol 69, No 5, 1991, pp549-55
14. Gilman, A.G., Rall, T.W., Nies, A.S., and Taylor, P., Goodman and Gilman's The *Pharmacological Basis of Therapeutics*, New York, Pergamon Press, (8th edn) 1990, p924
    Schorling, J.B., de Souza, M.A., and Guerrant, R.L., "Antibiotic use among children in an urban Brazilian slum: a risk factor for diarrhoea?", *American Journal of Public Health*, Vol 81, No 1, Jan 1991, pp99-100
    Laurence, D.R. and Bennett, P.N., *Clinical Pharmacology*, London, Churchill Livingstone, (6th edn), 1987, p638
15. AHRTAG, Preventing and Treating Diarrhoea in the Community, undated
    Popkin, B.M., Adair, L., Akin, J.S., et al, "Breast-feeding and diarrheal morbidity", *Pediatrics*, Vol 86, No 6, Dec 1990, pp874-82
    Victora, C.G., Vaughan, J.P., Lombardi, C., et al, "Evidence for protection by breast-feeding against infant deaths from infectious diseases in Brazil", *Lancet*, 8 Aug 1987, pp319-22
16. Feachem, R.G., "Prevention better than cure", *World Health*, Apr 1986, pp18-19
17. Rhode, J.E., "Selective Primary Health Care: Strategies for control of disease in the developing world. XV. Acute Diarrhoea", *Reviews of Infectious Diseases*, Vol 6, No 6, Nov-Dec 1984, pp840-54
18. UNICEF, WHO and UNESCO, *Facts for Life: A Communication Challenge*, New York, UNICEF, 1989, p19
19. Elarabi, I.I., "Where drugs don't help", *World Health*, Apr 1986, pp10-11
20. Laurence, D.R. and Bennett, P.N., op cit at note 14, p633
21. Santosham, M., Reid, R., "Diarrhoea management", *World Health*, Apr 1986, p8
    Claeson, M.E. and Clements, M.L., "Ridding the world of hydroxyquinolines", *British Medical Journal*, Vol 299, 26 Aug 1989, pp527-8
22. Wittenberg, D.F., Ramji, S., Broughton, M., "Oral rehydration therapy revisited", *Lancet*, Vol 337, No 8744, 30 Mar 1991, p798-9
23. Heymann, D.L., Mbvundula, M., Macheso, A., et al, "Oral rehydration therapy in Malawi: impact on the severity of disease and on hospital admissions, treatment practices and recurrent costs", *Bulletin of the World Health Organisation*, Vol 68, No 2, 1990, pp193-7
24. Phillips, M., Kumate-Rodríguez, J., and Mota-Hernández, F., "Costs of treating diarrhoea in a children's hospital in Mexico City", *Bulletin of the World Health Organization*, Vol 67, No 3, 1989, pp273-280
25. Hatch, D.L., Vreuls, R.C., Toole, M.J., et al, "The effective case management of childhood diarrhoea with oral rehydration therapy in the Kingdom of Lesotho", *International Journal of Epidemiology*, Vol 19, No 4, 1990, pp1066-71
26. El-Rafie, M., Hassouna, W.A., Hirschhorn, N., et al, "Effect of diarrhoeal disease control on infant and childhood mortality in Egypt: Report from the National Control of Diarrheal Diseases Project", *Lancet*, 10 Feb 1990, pp334-8
27. Carriere, R.C., "India: ORT survey", *Dialogue on Diarrhoea*, No 29, June 1987, p2
28. Soman, C.R., "Oral rehydration and the medical profession", *Dialogue on Diarrhoea*, No 29, June 1987, p8
29. Cruz, H., Paredes, P., and Haak, H., *Medicamentos Inapropiados en Diarrea: la magnitud del problema*, Lima, Peru, Pan-American Health Organisation, Nov 1989
30. Ibid., pp41-2
31. Phillips, M., Kumate-Rodríguez, J., and Mota-Hernández, F., op cit, pp276
32. Bhardwa, R.C., "Iran: attitudes to treatment and use of antibiotics", *Dialogue on Diarrhoea*, No 33, June 1988, p2
33. Nastasi, A., Massenti, M.F., Scarlata, G., et al, "A study on oral rehydration therapy of diarrheal disease in western Sicily", *European Journal of Epidemiology*, Vol 3, No 2, June 1987, pp151-4
34. Tomson, G., Sterky, G., "Self-prescribing by way of pharmacies in three Asian developing countries", *Lancet*, 13 Sep 1986, pp620-1
35. Yudkin, J.S., "Dispensing of inappropriate medicines for diarrhoea", *Lancet*, 31 Mar 1990, p803
36. Goodburn, E., Mattosinho, S., Mongi, P., et al, "Management of childhood diarrhoea by pharmacists and parents: Is Britain lagging behind the Third World?", *British Medical Journal*, Vol 302, 23 Feb 1991, pp440-3
37. Berih, A.A., McIntyre, I., Lynk, A.D., "Pharmacy dispensing practices for Sudanese children with diarrhoea", *Public Health*, Vol 103, 1989, pp455-8
38. WHO, *The treatment and prevention of acute diarrhoea: Practical Guidelines*, Geneva, WHO, (2nd edn) 1989
39. UNICEF, WHO and UNESCO, op cit at note 18, p47
40. UNICEF, *The State of the World's Children 1991*, Oxford and New York, Oxford University Press, 1990, p12
41. WHO, The rational use of ..., 1990, op cit, pp13 & 20
42. WHO, 1989, op cit, p4
43. Chetley, A., *Antibiotics: the wrong drugs for diarrhoea*, The Hague: HAI, 1987
44. Parish, P., *Medicines: a guide for everyone*, London, Penguin, (6th edn, revised), 1989, p144
45. WHO, 1989, op cit, p3
46. Balistreri, W.F., "Oral rehydration in acute infantile diarrhea", *American Journal of Medicine*, Vol 88 (Suppl 6A), 20 June 1990, pp6A:30S-33S
47. Gorbach, S.L., op cit at note 12, p1381
48. de Zoysa, I. and Feachem, R.G., "Interventions for the control of diarrhoeal diseases among young children: chemoprophylaxis", *Bulletin of the World Health Organization*, Vol 63, No 2, 1985, pp295-315
49. Based on a world market of US $438 million (a 1983-84 figure) for all antidiarrhoeal products, derived from industry sources, and from a calculation made by an industry representative at a 1983 workshop on diarrhoea held in Frankfurt, that 34% of the total world market in antidiarrhoeals was made up of antibiotics and other antimicrobial agents.
50. AMA, 1986, op cit at note 9, p964
51. Claeson, M.E. and Clements, M.L., op cit at note 21, pp527-8
52. WHO, 1989, op cit, p3
53. AMA, 1986, op cit at note 9, p971
54. Bhutta, T.I., "Agents for diarrhoea in children", *Lancet*, 337:8746, 13 Apr 1991, p925
55. Reynolds, J.E.F. (ed.), *Martindale: The Extra Pharmacopoeia*, London, The Pharmaceutical Press, (29th edn) 1989, p1582
56. Medawar C. and Freese, B., *Drug Diplomacy*, London, Social Audit, 1982, p51
57. Lanza, O. and Kerkvliet, E., *Ojo con los antidiarreicos: el abuso de antidiarreicos en America Latina*, Montevideo, AIS/IOCU, 1991, pp35-40

Chetley, A. *Problem Drugs*, Amsterdam,
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2B. Antidiarrhoeals containing antibiotics

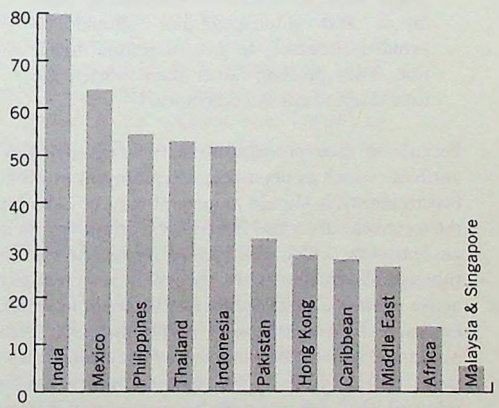
Antibiotics and diarrhoea: a dangerous combination

In November 1990, following two hard-hitting documentaries on British television, and a concerted international pressure campaign from Health Action International (HAI) and the Medical Lobby for Appropriate Marketing (MaLAM), the US-based company, Upjohn, agreed to phase out its antidiarrhoeal product, Kaomycin, worldwide over an 18-month period.

Kaomycin contained the antibiotic neomycin, as well as the adsorbents kaolin and pectin. As long ago as *1980* the World Health Organization (WHO) said unequivocally that neomycin "should *never* be used in the treatment of acute diarrhoea"[1] (original emphasis) because of its lack of efficacy in the treatment of acute diarrhoea, its ability to prolong or exacerbate diarrhoea, and its risk of side effects such as hearing damage or kidney failure.[2] Yet it took 10 years before one of the world's leading manufacturers of products containing neomycin began to take the product off the market. Even so, an Upjohn spokesman, John Butler, says that the company has never agreed with the stance of WHO that the use of neomycin in acute diarrhoea could be harmful. Instead, he says that the product was "simply eclipsed" by oral rehydration therapy. "It was purely a marketing decision".[3] As recently as 1989, Kaomycin was registered for use in 22 countries (including Germany), and Upjohn was doggedly defending it. The company said that it "would be irresponsible" to deny physicians access to such a product,[4] and that it had faith in the product's effectiveness and said that the benefits of use outweighed the small risk.[5]

Over the years, "marketing decisions", rather than public health decisions have led to the situation where, in many countries, a large proportion of products aimed at treating diarrhoea contain antibiotics or other antimicrobial drugs. A survey of antidiarrhoeal products carried out in 1989 found that nearly half of the 464 products listed in prescribing guides in 11 areas of the world contained an antimicrobial drug.[6] (See figure 2B-1.) A survey carried out in 1990 in 12

Figure 2B-1
Percentage of antidiarrhoeal products containing an antibiotic (1988-89)*



*Mexico data are from 1987
Source: Chetley, A., *A Healthy Business? World Health and the Pharmaceutica Industry*, London, Zed Books, 1990, p79

countries in Latin America — Argentina, Bolivia, Brazil, Chile, Colombia, Costa Rica, Ecuador, Guatemala, Mexico, Peru, Uruguay and Venezuela — found that out of a total of 351 antidiarrhoeal preparations marketed, 63% contained one or more antibiotics.[7] In the Yemen, a survey of 25 pharmacies during 1984 and 1985 found that over 40% of the treatments recommended for acute diarrhoea for children contained neomycin.[8] Surveys in the Sudan in 1988,[9] in Kenya in 1989,[10] in Peru in 1989,[11] in India in 1986,[12] in Mexico between 1983 and 1986,[13] in Sicily during 1984 and 1985,[14] and in the Philippines in 1984[15] found similar high levels of indiscriminate use of antidiarrhoeals containing antibiotics.

The worst of a bad lot

The indiscriminate use of antimicrobial drugs encourages the development of resistant micro-organisms and alters the normal bacterial content of the gut, which can lead to possible fungal infections and the overgrowth of resistant bacteria, can increase the risk of relapse, prolong the period when the patient with an infection can pass on the disease, and can also interfere with subsequent bacteriological diagnosis.[16]

Products containing neomycin, streptomycin or dihydrostreptomycin, chloramphenicol, and/or one of the many sulphonamides are of particular concern. The *British National Formulary*, which includes no combination antidiarrhoeal products containing antibiotics, points out that:

> "antibiotics and sulphonamides are generally unnecessary in simple gastroenteritis, even where a bacterial cause is suspected, because the complaint will usually resolve quickly without such treatment.... The general use of sulphonamides in treating diarrhoea of travellers is inadvisable because of the risks of rash and agranulocytosis. Poorly absorbed drugs such as dihydrostreptomycin, neomycin and sulphaguanidine should be avoided altogether in gastrointestinal infection. They prolong rather than shorten the time taken to control diarrhoea."[17]

Because of their potential toxicity, aminoglycoside antibiotics such as neomycin, streptomycin or dihydrostreptomycin should in general only be used for the treatment of *serious* infections.[18] Streptomycin is an antibiotic which still has an important role in tuberculosis treatment. In theory, it is potentially active against a large number of bacteria; however, extensive use and misuse of streptomycin has been associated with the development of widespread resistance to the drug by the bacteria which causes tuberculosis.[19] Because dihydrostreptomycin is more likely than streptomycin to cause partial or complete hearing loss, it is rarely used.[20]

Antimicrobials and sulphonamides found in antidiarrhoeal preparations

bacitracin
chloramphenicol
clefamide
colistin
dihydrostreptomycin
diloxanide furoate
framycetin
furazolidone
metronidazole
nalidixic acid
neomycin
nifuroxazide
oxytetracycline
paromomycin
phthalylsulphacetamide
phthalylsulphathiazole
piromidic acid
polymyxin B
polynoxylin
salicylazosulphapyridine
streptomycin
succinylsulphathiazole
sulphadimidine
sulphadiazine
sulphaguanidine
sulphaguanole
sulphamethoxazole
sulphasalazine
sulphathiazole
trimethoprim

The World Health Organization says quite clearly, as a result of a careful review of the most up-to-date scientific literature, that there is no evidence that neomycin, streptomycin or dihydrostreptomycin are effective in the treatment of diarrhoea, no matter what the cause of the diarrhoea might be.[21] Instead, they divert attention and resources from the more important aspects of diarrhoea therapy: rehydration, proper nutrition, appropriate antibiotics for the treatment of dysentery. As WHO puts it: "the production and sale of these products cannot be justified."[22]

Chloramphenicol is a powerful, inexpensive antibiotic which unfortunately is perhaps best known for its ability to provoke life-threatening blood disorders (aplastic anaemia), and "should only be given when there is no suitable alternative and never for minor infections".[23] The latest edition of *Goodman and Gilman's The Pharmacological Basis of Therapeutics* points out in large type that chloramphenicol "should never be employed in undefined situations or in diseases readily,

varied". The overall incidence of adverse reactions is about 5%.[30] The WHO has concluded that because of the lack of efficacy and concerns about safety,

> "there is no justification for the use of non-absorbable sulfonamides, or of systemically absorbed sulfonamides other than co-trimoxazole [sulphamethoxazole and trimethoprim], to treat diarrhoea or dysentery."[31]

Combining useful antimicrobials with ineffective ingredients

In the small proportion of diarrhoeas where an antimicrobial is required, such as for *Shigella* dysentery, amoebic dysentery, giardiasis, or possibly in *severe* cholera, WHO has prepared guidelines on which drugs to use. For *severe* cholera the first choice drug is tetracycline, with furazolidone, or trimethoprim-sulfamethoxazole (co-trimoxazole) as alternatives. For *Shigella* dysentery, the drug of choice is co-trimoxazole, with nalidixic acid or ampicillin as alternatives. For amoebic dysentery and giardiasis the drug of choice is metronidazole, with dehydroemetine hydrochloride as an alternative for *severe* amoebic dysentery, and quinacrine an alternative for giardiasis.[32]

Some of these drugs are often promoted for *any* type of "bacterial diarrhoea" or simply for "diarrhoea". Often, too, they are combined with other products such as kaolin, pectin, hydroxyquinolines, attapulgite, bismuth, or with other antimicrobials. A study of pharmacies in Asia found that in Bangladesh, for example, well over half the pharmacies recommended furazolidone, usually combined with kaolin and pectin, as the treatment for an 11-month old baby with non-specific diarrhoea.[33]

Once again, "marketing decisions" rather than public health decisions have led to this unnecessary use of antibiotics.

Most of the other antimicrobials that are regularly included in antidiarrhoeal preparations are of dubious value:

- **Bacitracin** is *perhaps* useful in the treatment of antibiotic-caused diarrhoea although vancomycin is preferred.[34]
- **Clefamide** is a minor antiprotozoal drug which has been used in the treatment of intestinal amoebiasis.[35]
- **Colistin** and **polymyxin B**, because of their toxic effects on the liver, are now rarely used.[36] They are not the drugs of first choice for the treatment of *any* specific infection.[37]
- **Diloxanide furoate** is the drug of choice for chronic intestinal amoebiasis in which only cysts are present.[38] However, in other forms of amoebic dysentery, metronidazole is the most effective drug.
- **Framycetin** has similar actions and uses as neomycin,[39] and its use in the treatment of diarrhoea is extremely doubtful.
- **Nifuroxazide** is a urinary tract antiseptic with a similarity to furazolidone. Although it has been used in the treatment of colitis and diarrhoea[40], there is little evidence of effectiveness.
- **Piromidic acid** and **nalidixic acid** have similar action and use, but piromidic acid is less active.[41] Like nalidixic acid, its primary use is for urinary tract infections, although it might conceivably have a very minor use in some cases of bacillary dysentery.
- **Polynoxylin** is a disinfectant which has antibacterial and antifungal action and is used in a variety of preparations for the local treatment of minor infections.[42] There is no recorded information about its value in treating diarrhoea.
- **Trimethoprim** is now rarely used on its own for diarrhoeas, although it may be useful in some cases of *Shigella* dysentery.[43] However, it is more common to find co-trimoxazole recommended.
- **Paromomycin** is used only to treat two parasitic diseases: tapeworm infestation and intestinal amoebiasis,[44] although it is by no means infallible in the latter case.[45] Side effects are mainly limited to gastrointestinal upset and diarrhoea.[46] Yet, in August 1986 Warner Lambert/Parke-Davis claimed in an advertisement in the *Philippines Index of Medical Specialities* that its brand of paromomycin with kaolin and pectin (Humagel) "stops diarrhoea fast". The product was indicated for all "specific and non-specific infectious diarrhoea caused by pathogens sensitive to paromomycin."

In this instance, and with many of the other antimicrobial drugs which have a specific, and very limited, use in the treatment of diarrhoea, companies have attempted to broaden the possible uses in their promotional materials. Such practice is far removed from the aims contained in the code of practice drawn up by the International Federation of Pharmaceutical Manufacturers Associations (IFPMA) which states that the pharmaceutical industry should provide only products which "have full regard to the needs of public health".

Before there can be better management of diarrhoea, the market needs to be cleansed of the large numbers of so-called antidiarrhoeal products that contain antibiotics. Over the past 10 years, HAI and many of the individual groups in the network have focused on antidiarrhoeal products as a key area for change, with some success.

In November 1986, the Italian pharmaceutical firm, Farmitalia Carlo Erba, announced that it was withdrawing three of its antidiarrhoeal products from the market worldwide, following concerted pressure from a UK-based justice and peace group. The three products – Quemiciclina, Mebinol Complex, and Entero-Pristina – had one thing in common: they all contained antimicrobials. A Carlo Erba spokesperson conceded that the drugs were "obsolete and no longer defensible from a medical point of view".[46]

safely, and effectively treatable with other antimicrobial agents".[24] It is generally reserved for the treatment of typhoid and paratyphoid fever and for meningitis.[25] Because it is an inexpensive drug, because it is easy to administer, and because if used correctly for a serious condition such as meningitis, the risk of fatal side effects is lower than the risk of death from meningitis,[26] chloramphenicol should be reserved for use in severe infections, particularly in developing countries. As a leading textbook, *Antibiotics in the Tropics*, says: "chloramphenicol should not be given in trivial infections which can be treated safely with less dangerous agents".[27]

The first sulphonamide was marketed in the mid-1930s. Since then many sulphonamides have been developed and they usually function by interfering with the ability of the bacteria to grow (bacteriostatic). Their broad spectrum of activity, however, has become limited because of the spread of resistance and the clinical use of sulphonamides therefore has declined.[28] Sulphonamides that are poorly absorbed from the gastroinrestinal tract — such as sulphaguanidine, succinylsulphathiazole and phthalylsulphathiazole — have a long history of being used for the treatment of diarrhoea. However, evidence of their efficacy is lacking.[29] In addition, side effects "are numerous and

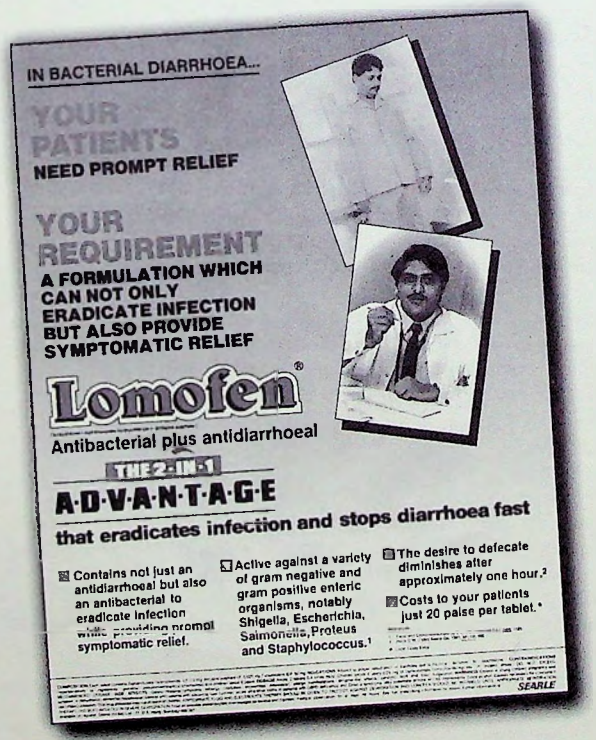
Travellers' diarrhoea

Acute diarrhoea, which in most cases is a mild illness lasting less than a week, occurs in 20-50% of travellers to developing countries.[1] Several studies have demonstrated that antibiotics can be used successfully to prevent travellers' diarrhoea.[2] Despite this, the consensus opinion is that there is little need to use antibiotics in this way. In the words of the American Medical Association (AMA):

> "Although effective chemoprophylactic regimens... are available, antimicrobial agents are not recommended for the prevention of travelers' diarrhoea because the risks associated with widespread administration of these agents outweigh the benefits of preventing an illness that usually is mild and self-limiting. These risks include the potential for: (1) serious adverse drug reactions; (2) the development of superinfections; and (3) the emergence of widespread bacterial resistance to the antimicrobial agents being used.[3]"

The best therapy is to be aware of and avoid possible sources of bacterial contamination in food and drink, make use of oral rehydration if diarrhoea develops, and seek early medical treatment if severe diarrhoea occurs with serious fluid loss and/or with blood or mucus.

Sources:
1. Studemeister, A., "Travel medicine for the primary care physician", *Western Journal of Medicine*, Vol 154, Apr 1991, pp418-22
Anon., "Preventing travellers' diarrhoea", *Lancet*, 16 July 1988, p144
2. Wistrom, J. and Norrby, R., "Antibiotic prophylaxis of travellers' diarrhoea", *Scandinavian Journal of Infectious Diseases*, Vol 70, (Suppl.), 1990, pp111-29
Taylor, D.N., Sanchez, J.L., Candler, W., et al, "Treatment of travelers' diarrhea: ciprofloxacin plus loperamide compared with ciprofloxacin alone: a placebo-controlled, randomized trial", *Annals of Internal Medicine*, Vol 114, No 9, 1 May 1991, pp731-4
Holtz, T.H. and Nettleman, M.D., "Emporiatrics: Diarrhea in travelers", *Infection Control and Hospital Epidemiology*, Vol 11, No 11, 1990, pp606-10
Ericsson, C.D., DuPont, H.L., Mathewson, J.J., et al, "Treatment of traveler's diarrhea with sulfamethoxazole and trimethoprim and loperamide", *Journal of the American Medical Association*, Vol 263, No 2, 12 Jan 1990, pp257-61
3. AMA, *Drug Evaluations*, Philadelphia, W.B. Saunders Co., (6th edn) 1986, p1277



Advertisement for a combination product containing furazolidone, diphenoxylate and atropine (Lomofen) in Searle's Diarrhoea Update, India, 1991

Michael Rawlins, professor of clinical pharmacology at Newcastle University, said of the products, "it is outrageous even to consider marketing such drugs for diarrhoea in this day and age".[48]

In 1984, the best selling antidiarrhoeal drug in the Philippines was Parke-Davis' Chlorostrep, a combination of chloramphenicol and streptomycin.[49] Similarly in India, it was a popular product. Following campaigns by the Drug Action Forum in India and by the Medical Lobby for Appropriate Marketing (MaLAM), Parke-Davis announced in 1987 that "Chlorostrep would cease to exist in 1987".[50]

Correspondence from MaLAM to SmithKline in 1986 and 1987 drew attention to advertising in Pakistan, Indonesia and India which promoted the company's Furoxone (furazolidone, kaolin and pectin) and Dependal-M (furazolidone, metronidazole, kaolin and pectin) for non-specific diarrhoea. SmithKline first reluctantly agreed to modify its advertising claims and ultimately recognised that the formulation was irrational and has subsequently dropped the kaolin and pectin.

Despite those successes, there is still much to be done. For example, 18 of the 39 antidiarrhoeal preparations listed in the *Philippines Index of Medical Specialities* in January 1991 contained an antibiotic, and 11 of those 18 were combination products.[51] One of those products, Wyeth's Polymagma (streptomycin, polymyxin B, attapulgite, pectin and aluminium hydroxide), was being promoted in the Philippines as "the antidiarrhoeal for all seasons, for all patients. Proven efficacy against acute infectious diarrhoea".[52] Wyeth subsequently announced that it had begun a global discontinuation programme for antidiarrhoeals that contain antibiotics, and that it expected that all outstanding stocks of Polymagma would disappear by mid-1992.

With advertising such as this, for products that have little or no regard for public health, the time is long overdue for much stronger measures to be taken. It is clear that nearly half the antidiarrhoeal products now on the market could and should be withdrawn because they contain an unnecessary antimicrobial. If the pharmaceutical industry is not prepared to withdraw those products voluntarily, then it is up to governments and their regulatory authorities to prohibit their sale.

Recommendation for action

Antidiarrhoeal products containing neomycin, streptomycin/dihydrostreptomycin, chloramphenicol, or nonabsorbable sulphonamides, should be taken off the market *immediately*.

Notes and references:

1. WHO, *A Manual for the Treatment of Acute Diarrhoea*, Doc No WHO/CDD/SER/80.2, Geneva, 1980, p13
2. WHO, *The rational use of drugs in the management of acute diarrhoea in children*, Geneva, WHO, 1990, pp31 & 33
3. Scanlon, C., "Unsafe drugs find buyers abroad", *Detroit Free Press*, 20 May 1991, p4A
4. Anon., "Antidiarrhoeals again under attack", *Scrip*, No 1457, 20 Oct 1989, p29
5. Anon., "Misuse of antidiarrhoeal medicines", *Lancet*, 21 Oct 1989
6. Chetley, A., *A Healthy Business? World Health and the Pharmaceutical Industry*, London, Zed Books, 1990, p79
7. Lanza, O. and Kerkvliet, E., *Ojo con los antidiarreicos: el abuso de antidiarreicos en América Latina*, Montevideo, AIS/IOCU, 1991, pp35-40
8. Tomson, G., Sterky, G., "Self-prescribing by way of pharmacies in three Asian developing countries", *Lancet*, 13 Sep 1986, pp620-1
9. Berih, A.A., McIntyre, L., Lynk, A.D., "Pharmacy dispensing practices for Sudanese children with diarrhoea", *Public Health*, Vol 103, 1989, pp455-8
10. Yudkin, J.S., "Dispensing of inappropriate medicines for diarrhoea", *Lancet*, 31 Mar 1990, p803
11. Cruz, H., Paredes, P., and Haak, H., *Medicamentos Inapropiados en Diarrea: La magnitud del problema*, Lima, Peru, Pan-American Health Organisation, Nov 1989
12. Carriere, R.C., "India: ORT survey", *Dialogue on Diarrhoea*, No 29, June 1987, p2
13. Phillips, M., Kumate-Rodriguez, J., and Mota-Hernández, F., "Costs of treating diarrhoea in a children's hospital in Mexico City", *Bulletin of the World Health Organization*, 67:3, 1989, pp276
14. Nastasi, A., Massenti, M.F., Scarlata, G., et al, "A study on oral rehydration therapy of diarrheal disease in western Sicily", *European Journal of Epidemiology*, Vol 3, No 2, June 1987, pp151-4
15. Quanico, U.T., "Antidiarrhoeals in the Philippines", *The Drug Monitor*, Vol 2, No 6, June 1987 (117 out of 194 antidiarrhoeal products were found to contain antibiotics); see also: Tan, M.L., *Dying for Drugs*, Manila, Health Action Information Network, 1988, pp85-88
16. Parish, P., *Medicines: a guide for everybody*, London, Penguin (6th edn, revised), 1989, p144
17. BMA and the Royal Pharmaceutical Society of Great Britain, *British National Formulary*, London, BMA and The Pharmaceutical Press, No 21, March 1991, p36
18. Reynolds, J.E.F. (ed.), *Martindale: The Extra Pharmacopoeia*, London, The Pharmaceutical Press, (29th edn) 1989, p105
19. WHO, 1990, op cit, pp25-6
20. Reynolds, J.E.F., op cit, p216
21. WHO, 1990, op cit, pp28 & 34
22. Ibid.
23. Reynolds, J.E.F., op cit, p106
24. Gilman, A.G., Rall, T.W., Nies, A.S., and Taylor, P., *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, New York, Pergamon Press, (8th edn) 1990, p1128
25. Pratt, W.B. and Fekety, R., *The Antimicrobial Drugs*, Oxford, Oxford University Press, 1986, p193
26. Pecoul, B., Varaine, F., et al, "Long-acting chloramphenicol versus intravenous ampicillin for treatment of bacterial meningitis", *Lancet*, Vol 338, No 8771, 5 Oct 1991, pp862-6
27. Enenkel, S. and Stille, W., *Antibiotics in the Tropics: antibacterial therapy with limited resources*, Berlin, Springer-Verlag, 1988, p14
28. Reynolds, J.E.F. op cit, p108
29. WHO, 1990, op cit, pp43-9
30. Gilman, A.G., op cit, p1052
31. WHO, 1990, op cit, p48
32. Ibid., p3
33. Tomson, G., op cit
34. Pratt, W.B., op cit, p144
35. Reynolds, J.E.F., op cit, p661
36. Gilman, A.G., op cit, p1138
37. Pratt, W.B., op cit, p255
38. BMA, op cit, p225
39. Reynolds, J.E.F., op cit, p234
40. Reynolds, J.E.F., op cit, p 1595
41. Ibid., p288
42. Ibid., p968
43. Salam, M.A. and Bennish, M.L., "Antimicrobial therapy for Shigellosis", *Reviews of Infectious Diseases*, Vol 12, Suppl 4, Mar-Apr 1991, pS336
44. Pratt, W.B., op cit, p153
45. Gilman, A.G., op cit, p1006
46. Ibid.
47. O'Sullivan, J., "Pills for profit or saving lives?", *Catholic Herald*, 14 Nov 1986
48. Ibid.
49. Quanico, U.T., "Antidiarrhoeals in the Philippines", *The Drug Monitor*, Vol 2, No 6, June 1987, p10
50. Anon., "Parke-Davis/Warner Lambert: Oral streptomycin chloramphenicol combination", *MaLAM Newsletter*, Jun 1987
51. Anon., "Antidiarrheals in the Philippines — How safe, how effective?", *The Drug Monitor*, Vol VI, No 3, Mar 1991, p35
52. Letter from MaLAM to Wyeth, July 1991. See: *MaLAM Newsletter*, Nov 1991.

Chetley, A. *Problem Drugs*, Amsterdam, Health Action International, 1993

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2C. Hydroxyquinolines

Worldwide withdrawal... overdue for 20 years

When 19-year-old Mieko Hoshi came down with diarrhoea in June 1969 and doctors were having trouble controlling it, she was eventually given a halogenated hydroxyquinoline drug called iodochlorhydroxyquin (or clioquinol). Shortly afterwards, she suffered from a temporary paralysis of her facial muscles, causing her to lose the ability to speak for a few days. When that problem disappeared, she began to suffer from a growing numbness in her legs which spread to an almost complete paralysis of her body. In October 1969 she also lost her eyesight. By the beginning of 1970 it was clear that Mieko was one of the more than 11,000 victims of a disease called subacute myelo-optic neuropathy (SMON) that swept through Japan between 1955 and 1970.[1]

It took much of this time to uncover the cause of the disease. On 7 August 1970, Japanese scientists reported that clioquinol was the probable cause. Within a month, the Japanese government banned all of the 186 halogenated hydroxyquinolines products on the market.[2]

Clioquinol was the active ingredient in widely-used antidiarrhoeal drugs such as Entero-Vioform and Mexaform, marketed by the Swiss company, Ciba-Geigy. Ciba first marketed clioquinol in 1900 as a powder for wounds under the name of Vioform. In 1934, Ciba introduced it for oral use as Entero-Vioform. Only one year after it was put on the market, Ciba received a report from doctors in Argentina describing the same side effects as the later Japanese cases. Animal trials in the late 1930s showed that the drug caused convulsions in cats, some of which were fatal. In the early 1960s, Ciba-Geigy received studies showing that dogs with diarrhoea, when treated with Entero-Vioform, died in seizures. In 1966, Dr Olle Hansson of Sweden, in collaboration with a Swedish ophthalmologist, published a report in *The Lancet* on the optic atrophy and blindness caused by the drug. In 1972, Japanese victims began to take legal action against Ciba-Geigy, but it was not until six years later that the company both apologised to them, and paid substantial damages.[3]

However, Ciba-Geigy refused to concede that the drug was dangerous. In a 1980 press release the company claimed "there is no conclusive scientific evidence that clioquinol causes SMON."[4] The press release said that agreeing to settle the claims for damages in Japan was "not inconsistent with the decision to continue to offer products containing clioquinol. In view of the extreme rarity of clioquinol side-effects outside Japan, Ciba-Geigy considers that one or more additional factors played a part in the 1955-70 SMON epidemic in Japan.... Used as directed, products such as Entero-Vioform and Mexaform are both safe and reliable."

Medical opinion disagreed with Ciba-Geigy.[5] Clinicians from England, Australia, Switzerland, Sweden, Denmark, the Netherlands and the United States have described patients who developed neurologic symptoms while taking iodochlorhydroxyquin, di-iodohydroxyquin or broxyquinoline. The clinical symptoms of these patients and the dosages and length of therapy were similar to those noted in the histories of Japanese patients with SMON.[6] As well as an increasing amount of evidence to link the hydroxyquinolines with SMON, doubt was also emerging about the efficacy of these products in the treatment of diarrhoea. One researcher notes the lack of experimental evidence of efficacy for the use of hydroxyquinolines:

> "In fact, these agents appear to be of no value in any but amoebic diarrhoea, and even then are not drugs of choice. Drug toxicity with retinal degeneration has proved a high risk for such an ineffective agent."[7]

The American Medical Association states:

> "Clioquinol (iodochlorhydroxyquin) and iodoquinol (diiodohydroxyquin) have been used in the prophylaxis of travellers' diarrhea but proof of their efficacy is lacking.... The indiscriminate use of such potentially toxic agents is unjustified."[8]

The authoritative *Martindale* guide to medicines notes, somewhat optimistically, that "most oral preparations of halogenated hydroxyquinolines have been withdrawn since the association between clioquinol and subacute myelo-optic neuropathy (SMON) was established".[9]

All of the companies have been inexcusably slow in removing these hazardous drugs. Ciba-Geigy, under pressure since the early 1970s, finally announced in November 1982 its intention to "phase out" the production and sale of clioquinol oral preparations over a three to five year period. The company still maintained the decision was not related to the drug's toxicity, but rather reflected new developments in diarrhoeal disease control. Dr Olle Hansson said the decision came "15 years too late" and also, once taken, should have been effective immediately.[10] In November 1984 Ciba-Geigy announced that it would "accelerate" its original policy and stop the supply of the products "by the end of the first quarter of 1985".[11]

Dr Andrew Herxheimer, a senior clinical pharmacologist in the UK, explained that because clioquinol was such a profitable drug for decades, when it was found to cause disastrous neurological damage, the company found itself in a dilemma. "Withdrawal of the drug would have weakened its legal position. This was probably a major reason for the company's policy of persistent denial of the drug's hazards and continued assertion of its value," said Dr Herxheimer. He added that the 1982 announcement about a

Table 2C-1
Hydroxyquinolines available in 1988-89 in selected countries
Product Brand Name (Company Name) – ingredients

Products containing clioquinol:

India:

Aldiamycin (Alkem) – clioquinol, streptomycin, phthalylsulphathiazole, pectin
Dysfur Plus (Biological E) – clioquinol, furazolidone, atropine

Indonesia:*

Bintaform (Bintang T)
Diarent (Kenrose) – clioquinol, phthalylsulphathiazole, papaverine, B vitamins, bismuth carbonate
Diarent sp. (Kenrose) – clioquinol, phthalylsulphathiazole, kaolin, B vitamins, bismuth carbonate, tanin albuminate
Diastop (Conmed) – clioquinol, phthalylsulphathiazole, kaolin, papaverine, B vitamins
Diastop syrup (Conmed) – clioquinol, phthalylsulphathiazole, kaolin, pectin, B vitamins
Enterobiotic (New Interbat) – clioquinol, neomycin, furazolidone, kaolin, pectin, papaverine
Enterodiastop (Combiphar) – clioquinol, phthalylsulphathiazole, papaverine, B vitamins
Enterosept (Soho) – clioquinol
Enteroviosulfa (Kimia Farma) – clioquinol, sulphaguanidine, papaverine, B vitamins
Himaform Sulfa (Himajaya) – clioquinol, sulphaguanidine, belladonna, papaverine, B vitamins
Koniform (Konimex) – clioquinol, phthalylsulphathiazole, papaverine, chlorpheniramine
Libroform (Bin. Toedjoe) – clioquinol, sulphadimidine, belladonna, chloroquin
Nifural (Pharos Chemie) – clioquinol, nifuroxazide
Sulfa Plus (Nellco) – clioquinol, sulphaguanidine, papaverine, B vitamins
Viostreptin (Bernofarm) – clioquinol, streptomycin, sulphaguanidine, kaolin, B vitamins
Viosulfon (Pharos Indon.) – clioquinol, phthalylsulphathiazole, vitamin K, papaverine, bismuth carbonate

Mexico (1987):

Di-Sulkin (Arlex) – clioquinol, pectin, dimethicone
Solfurol (Solfran) – clioquinol, furazolidone, kaolin, pectin, homatropine methylbromide
Suyodil (Farmacos Cont) – clioquinol, kaolin, pectin
Viotalidina (Carnot) – clioquinol, phthalylsulphathiazole
Yosul (Riger's) – clioquinol, papaverine, charcoal
Yosul sp (Riger's) – clioquinol, kaolin, pectin, homatropine methylbromide

Middle East:

Entox (Wyeth) – clioquinol, dihydrostreptomycin, attapulgite

Thailand:

Chlorotracin (Chew Bros.) – clioquinol, chloramphenicol, phthalylsulphathiazole
Quinoxthaline (T P Drug Lab) – clioquinol, phthalylsulphathiazole
Vanoform (Vana) – clioquinol, neomycin, phthalylsulphathiazole, furazolidone, kaolin, homatropine methylbromide

phased withdrawal "may save face but at the cost of more years of ineffective hazardous medication. Clioquinol already holds the scandalous record of delay – 12 years – between the occurrence of a major drug disaster and its effective prevention. Why then add another 3 to 5 years? For all manufacturers and distributors of hydroxyquinolines the message is clear: stop now."[12]

Of any use?

Table 2C-1 gives some indication of the large number of hydroxyquinoline products still on the market in 1988-9 as antidiarrhoeals. More than 60 were found in prescribing guides in Asia, the Middle East, and Latin America. A survey carried out in 1990 in 12 Latin American countries - Argentina, Bolivia, Brazil, Chile, Colombia, Costa Rica, Ecuador, Guatemala, Mexico, Peru, Uruguay and Venezuela - found that 12% of the total of 351 antidiarrhoeal preparations marketed contained clioquinol or another hydroxyquinoline.[13] Most of the products in both surveys also contain other ingredients such as phthalylsulphathiazole, streptomycin, neomycin, and sulphaguanidine which should be avoided in gastrointestinal infection because they can prolong rather than shorten the time taken to control diarrhoea.[14]

Clioquinol and the other hydroxyquinolines are also sometimes used in skin creams and ointments to treat various types of skin rashes. Once again, their use is

Table 2C-1

Products containing other hydroxyquinolines:

India:

Amicline Plus (Griffon) – di-iodohydroxyquin, oxytetracycline, chloroquin
Chlorambin (AFD) – di-iodohydroxyquin, neomycin, kaolin, pectin, belladonna
Chlorambin tablet (AFD) – di-iodohydroxyquin, metronidazole
Saril (Rallis) – di-iodohydroxyquin, streptomycin, phthalylsulphathiazole, pectin, tanin albuminate

Indonesia:*

Diarex tablet (Pharmac Apex) – di-iodohydroxyquin, streptomycin, bacitracin, kaolin, pectin, vitamin K
Diarex suspension (Pharmac Apex) – di-iodohydroxyquin, streptomycin, phthalylsulphathiazole, kaolin, sodium citrate, B vitamins
Quixalin (Squibb) – halquinol

Mexico (1987):

Bontal (Farmacos Cont) – di-iodohydroxyquin, phthalylsulphathiazole, charcoal, homatropine methylbromide
Colfur (Wallace) – di-iodohydroxyquin, colistin, furazolidone, dicyclomine
Diarim (Rimsa) – di-iodohydroxyquin, furazolidone, pectin, attapulgite, homatropine methylbromide
Dipec (Yauquimia) – di-iodohydroxyquin, furazolidone, kaolin, pectin, homatropine methylbromide
Entero Diyod (Serral) – di-iodohydroxyquin
Entero Diyod Compuesto (Serral) – di-iodohydroxyquin, succinylsulphathiazole, papaverine
Enterocarbin (Index) – di-iodohydroxyquin, succinylsulphathiazole, phthalylsulphathiazole, charcoal, homatropine methylbromide
Oxibeldina tablets (Lagesa) – di-iodohydroxyquin, phthalylsulphathiazole, belladonna
Oxibeldina suspension (Lagesa) – di-iodohydroxyquin, phthalylsulphathiazole, homatropine methylbromide
Prometac (Provit) – di-iodohydroxyquin, phthalylsulphathiazole, homatropine methylbromide
Stopen (Berman) – di-iodohydroxyquin, phthalylsulphathiazole, kaolin, pectin, homatropine methylbromide
Vioftalyl (Bigaux) – di-iodohydroxyquin, phthalylsulphathiazole, pectin
Vioftalyl suspension (Bigaux) – di-iodohydroxyquin, phthalylsulphathiazole, pectin, scopolia extract
Zetaquin (Kener) – di-iodohydroxyquin, phthalylsulphathiazole, homatropine methylbromide

Pakistan:

Di-iodohydroxyquin (Ethical)
Di-iodohydroxyquin (PVP)
Di-iodohydroxyquin (Sibro)
Di-iodohydroxyquin (Unexo)
Diodoquin (Searle) – di-iodohydroxyquin
Diodoquin suspension (Searle) – di-iodohydroxyquin

Thailand:

Coccila (Thai Nakorn P.) – di-iodohydroxyquin, neomycin, phthalylsulphathiazole, furazolidone, kaolin
Dia-Fucin (Greater Phar.) – di-iodohydroxyquin, neomycin, phthalylsulphathiazole, furazolidone, kaolin
Diolin (Chinta) – di-iodohydroxyquin, furazolidone, kaolin, pectin, atropine
Disento (Nakorn Patana) – di-iodohydroxyquin, neomycin, phthalylsulphathiazole, furazolidone, kaolin
Mediocin (Medical Sup.) – di-iodohydroxyquin, phthalylsulphathiazole, furazolidone
Neomobin (Osoth) – di-iodohydroxyquin, neomycin, phthalylsulphathiazole

Sources: *Indonesian Index of Medical Specialities* (Oct 1988); *MIMS India* (Feb 1988); *MIMS Middle East* (Dec 1989); *Diccionario de Especialidades Farmaceuticas* (Mexico, 1987); *Quick Index of Medical Preparations* (Pakistan, 1988-9); *Thailand Index of Medical Specialities* (Nov 1988)
Notes: *In October 1991, the government of Indonesia deregistered 94 antidiarrhoeal products, including many which contained hydroxyquinolines. For further information, see: Anon., "Daftar 285 Obat Yang Ditarik Dari Peredaran" (List of 285 drugs which are withdrawn from circulation). *Suara Pembaruan*, 29 Oct 1991.

doubtful. Clioquinol has been used in the treatment of the rare childhood skin condition, acrodermatitis enteropathica. It has been established since 1973 that treatment with zinc salts is more effective and safer.[13]

Recent animal and human studies in the USA show that clioquinol used in skin creams for the treatment of diaper rash and other skin problems is readily absorbed into the body. In the animal studies, all treated dogs lost weight, became lethargic and less responsive to stimuli and four that were examined were found to have suffered liver damage. One dog died after 15 days of treatment and another experienced hind limb paralysis. The authors of the study noted that this paralysis was identical to that reported in a study of oral administration of clioquinol. The authors concluded that long-term application of the drugs to the skin, particularly in the treatment of diaper rash, could lead to liver damage.[16]

Time to act

Japan has banned all hydroxyquinolines. Some other governments have also taken action over these drugs. *Clioquinol* is banned in Dominican Republic, Honduras, Nepal, US, Malaysia, Pakistan, Spain, Zimbabwe; withdrawn in Italy, Norway, the Netherlands, Sweden; its import into Saudi Arabia is prohibited, and is subject to restriction in Australia, Cuba, France, UK, Switzerland and Zambia. *All hydroxyquinoline derivatives* are banned in Bangladesh and have been withdrawn in Cyprus, Denmark, Italy, Philippines, Turkey, and subject to restriction in Venezuela.[17]

The danger of not banning *all* the hydroxyquinolines is evident from the example of what happened in Pakistan. After a government ban on clioquinol products in February 1984 forced the withdrawal of Entox, produced by US-based Wyeth/American Home Products, the company relaunched the drug in August 1984 in a "clioquinol-free" formulation. The clioquinol was replaced with di-iodohydroxyquin. Company literature put out at the time said it was a "convenient, easily swallowed tablet for most forms of diarrhoea".[18] Subsequently, Wyeth again reformulated the product, and by 1990 it simply contained attapulgite, an ineffective adsorbent.

The continuing threat to health caused by the hydroxyquinolines demands further swift action. In the words of Drs Hansson and Herxheimer, as long ago as 1984,

> "a worldwide withdrawal of all oral products containing halogenated hydroxyquinolines has been overdue for a decade."[19]

More recently, the World Health Organization was equally hard-hitting about the hydroxyquinolines:

> "The side-effects associated with hydroxyquinolines, while not common, can be severe. The use of these products in the treatment of acute diarrhoea and amoebiasis cannot be justified, and there is thus no rationale for their continued production and sale."[20]

[See also the sections on: *Antidiarrhoeals, Antibiotics, Diphenoxylate* and *Loperamide*.]

Recommendations for action

1. An immediate ban of all oral products containing halogenated hydroxyquinolines.
2. A suspension of all skin creams containing halogenated hydroxyquinolines unless new evidence reliably demonstrates that they are not toxic.

Notes and references:

1. Hansson, O., *Inside Ciba-Geigy*, Penang, International Organization of Consumers Unions, 1989, pp3-6 & 13
2. Ibid., pp6-10
3. Ibid., pp14-40
4. Anon., "Round the World", *Lancet*, 14 June 1980, p1293
5. Claeson, M.E. and Clements, M.L., "Ridding the world of hydroxyquinolines", *British Medical Journal*, Vol 299, 26 Aug 1989, pp527-8
6. Hansson, O., op cit, p44
7. Rohde, J. E., "Selective primary health care: strategies for control of disease in the developing world. XV. Acute diarrhoea", *Reviews of Infectious Diseases*, Vol 6, No 6, Nov-Dec 1984, pp840-54
8. AMA, *Drug Evaluations*, Philadelphia, W.B. Saunders Co., (6th edn) 1986, p964
9. Reynolds, J.E.F. (ed.), *Martindale: The Extra Pharmacopoeia*, London, The Pharmaceutical Press, (29th edn) 1989, p658
10. Anon., "Ciba-Geigy to 'phase-out' clioquinol", *HAI News*, No 8, Dec 1982
11. Hansson, O., op cit, p89
12. Herxheimer, A., "Clioquinol: A slow withdrawal is not good enough", *HAI News*, No 9, Feb 1983
13. Lanza, O. and Kerkvliet, E., *Ojo con los antidiarreicos: el abuso de antidiarreicos en América Latina*, Montevideo, AIS/IOCU, 1991, pp35-40
14. BMA and the Royal Pharmaceutical Society of Great Britain, *British National Formulary*, London, BMA and The Pharmaceutical Press, No 21, Mar 1991, p36
15. Anon., *Bad Information Means Bad Medicine*, London, Social Audit, 1981
16. Greenberg, A., et al, *Citizen's petition*, submitted to the US Food and Drug Administration, on behalf of the Public Citizen Health Research Group, 24 July 1985
17. United Nations, *Consolidated List of Products Whose Consumption and/or Sale Have Been Banned, Withdrawn, Severely Restricted or Not Approved by Governments*, 2nd Issue, Doc No ST/ESA/192, New York, 1987, pp29-30 & 75
    Anon., "The name of the game", *New Internationalist*, Apr 1981, p6
    Anon., "Ciba to withdraw clioquinol", *Utusan Konsumer*, Apr 1983
    Anon., "Clioquinol-free reformulated Entox now available", *Pharma News* (Karachi), 15-31 Aug 1984
    Anon. "Spain for rational drug use: 111 drugs banned", *HAI News*, No 14, Dec 1983
    Ahmad, S.R., *Bitter Facts About Drugs*, Karachi, HAI Pakistan, 1990, pp33-4
18. Hansson, O. and Herxheimer, A., "Halogenated hydroxyquinollnes: still no end", *Lancet*, 13 Oct 1984, p864
19. Ibid.
20. WHO, *The rational use of drugs in the management of acute diarrhoea in children*, Geneva, WHO, 1990, p40

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2D. Diphenoxylate

"*Not* an innocuous drug"[1]

In February 1988, the US-based G.D. Searle company invited Australian doctors who were prescribers of its antidiarrhoeal product, Lomotil (diphenoxylate and atropine), to enter a prize draw for a nine-day trip for two to the Olympics in Seoul, South Korea. The prize, which included the flights, accommodation and tickets to the opening ceremonies and other events, was valued at Aus $6,000. The president of the Royal Australian College of General Practitioners, Dr Eric Fisher, said:

"Advertisements like this one do not reflect credit on the drug company or the practitioners. The college cannot support any advertising which bears no relation to standards of patient care or which does little to increase the education of the prescriber."

Searle was found to be in breach of the Australian Pharmaceutical Manufacturers' Association code of conduct and was forced to cancel the promotion, after 6,000 doctors had responded.[2]

One of the two best-selling antidiarrhoeal drugs in the world, Lomotil was among the top 200 most prescribed drugs in the USA in 1988.[3] Lomotil acts as a constipating agent in a similar manner to opiates, focusing on the symptom, not the cause of the diarrhoea.[4] Other manufacturers of products containing diphenoxylate include Janssen (Reasec) and Cilag (Lyspafen).

In the USA, Lomotil carries a warning that it is "not an innocuous drug and dosage recommendations should be strictly adhered to, especially in children."[5] The warning is given because several cases of severe central nervous system toxicity have been reported with normal therapeutic doses and because overdose is common when repeated doses are taken for severe diarrhoea. Overdosage can result in coma or death. Even in older children there are problems.

This advertisement from the Philippines in October 1990 misinterprets data from a scientific study. It also tries to gain respectability by associating itself with astronauts: "so dependable even astronauts have carried it in space flights!" The 1991 edition of The Essential Guide to Prescription Drugs (Long, J.W., New York, HarperCollins), points out that the use of Lomotil "is a disqualification for piloting" and advises pilots of aircraft to consult with a designated Aviation Medical Examiner.

Diphenoxylate is also a common source of accidental poisoning in toddlers.[6] A 1983 report identified diphenoxylate as "an important cause of accidental poisoning in children under the age of five [in the UK]. Symptoms of overdosage in children can occur after as little as one tablet."[7]

As long ago as 1975, the dangers of using Lomotil for children were clearly recognised. "It can also mask the signs of dehydration and cause fatal toxic reactions.... Use of this combination [diphenoxylate and atropine] for treatment of diarrhoea in children is hazardous."[8] The World Health Organization (WHO) notes that preparations such as diphenoxylate "can be dangerous, and even fatal, if used incorrectly in infants".[9]

In 1981, after public exposure of this problem by the UK-based public interest group, Social Audit, Searle agreed to restrict the use of its product worldwide to children over two years of age.[10] In the UK, the product is not recommended for children under four;[11] however, most authoritative opinion agrees that Lomotil "should not be given to children".[12] For example, in Australia, parents are told, "Do not give this preparation to children under 12".[13]

An ineffective drug?

As well as being hazardous in children, there are serious doubts about the effectiveness of diphenoxylate. Lomotil will not relieve the underlying cause of the diarrhoea.[14] For example, diphenoxylate has been described as "the *worst* means of treating" infectious diarrhoea, because it can prolong the length of time that toxins from the bacteria remain in the intestinal tract.[15] The toxins destroy the lining of the intestinal tract, which in turn allows continued loss of fluids and increased dehydration. Most of the clinical trials that have been carried out on either adults or children show little or no signs of the efficacy of diphenoxylate.[16] Nonetheless, Searle uses such poor evidence to promote its product. For example, in the Philippines in October 1990, an advertisement for Lomotil quoted a 1987 study[17] as saying "Lomotil has a rapid onset of action, resulting in early relief of diarrhea". The advertisement failed to point out that although 80% of the patients who received diphenoxylate reported that the drug "helped a lot", so did 75% of patients receiving a placebo. The difference between the two groups was not statistically significant.[18] In other words, Lomotil was really no better than placebo in dealing with the diarrhoea, making the headline for the advertisement – "When diarrhea strikes, stop it fast with Lomotil" – a figment of a marketing manager's imagination rather than a scientifically valid finding.

After a careful review of the most up-to-date scientific evidence, WHO concluded that:

> "Diphenoxylate cannot be recommended for the management of diarrhoea in children, and there is thus no rationale for the production and sale of liquid and syrup formulations for paediatric use."[19]

[See also sections on: *Antidiarrhoeals*, *Antibiotics*, *Antidiarrhoeals containing antibiotics*, *Hydroxyquinolines*, and *Loperamide*.]

- **Generic name:** Diphenoxylate hydrochloride with atropine sulphate
- **Some brand names:** Lomotil (Searle); Reasec (Janssen); Lyspafen (Cilag)
- **Indications suggested by authoritative sources:** *Symptomatic* relief of non- infective acute diarrhoea as a secondary measure *after* initiation of rehydration therapy; non-routine use for *symptomatic* relief of some chronic diarrhoeas
- **Essential drug?:** Not on WHO's Essential Drug List
- **Contraindications suggested by authoritative sources:** impaired liver function;[20] antibiotic-induced diarrhoea;[21] sensitivity, jaundice, intestinal obstruction, acute ulcerative colitis;[22] acute infectious diarrhoea[23]
- **Use in pregnancy:** safety in pregnancy has not been established[24]
- **Breastfeeding:** the drug passes into the milk, best to avoid it[25]
- **Infants and children:** Do not give this preparation to children under 12;[26] cannot be recommended for the management of diarrhoea in children[27]
- **Elderly:** adverse reactions and side effects may be more frequent and severe[28]
- **Warnings:** Dosage recommendations should be strictly adhered to.
  Overdosage can cause severe respiratory depression and coma, possibly leading to permanent brain damage or death. Use only after rehydration therapy has been started.[29] Prolonged use is not advised, may be habit forming.[30]
- **Adverse reactions:** The incidence of adverse reactions is relatively low,[31] but the variety of adverse reactions reported include: numbness of the limbs, euphoria, depression, malaise, lethargy, confusion, sedation, drowsiness, dizziness, restlessness, headache, anaphylaxis, angioneurotic oedema, urticaria, swelling of the gums, pruritus, toxic megacolon, paralytic ileus, pancreatitis, vomiting, nausea, anorexia, abdominal discomfort, hyperthermia, tachycardia, urinary retention, flushing, dryness of the skin and mucous membranes.[32] Toxic megacolon is more likely to occur in severely ill or undernourished patients.[33]

Recommendations for action

1. All products containing diphenoxylate should be contraindicated in children.
2. All product information and advertising for products containing diphenoxylate should contain a warning that:
   a) oral rehydration therapy is the first-line treatment in most diarrhoeas;
   b) the product should not be used in acute diarrhoea;
   c) the product should not be used for pregnant and lactating women, the elderly, those with liver dysfunctions or jaundice, that it could be habit forming and that all dosage recommendations should be carefully followed;
   d) the product should not be used in the routine treatment of inflammatory bowel disease.
3. National regulatory authorities may wish to ban the use of this product as non-essential in the treatment of diarrhoea.

Notes and references:

1. *Physicians' Desk Reference*, Oradell, NJ, Medical Economics Company, 44th edn, 1990, p2069
2. The incident is described in Chetley, A., *A Healthy Business? World Health and the Pharmaceutical Industry*, London, Zed Books, 1990, pp60-1. The advertisements appeared in *Australian Doctor* (12 Feb 1988) and *Medical Observer* (17 Mar 1988). Reports of the incident appeared in: Totaro, P., 'Row as drug firm offers doctors prize', *Daily Telegraph* (Australia), 29 Apr 1988; McDonnell, D., 'Drug company in offer uproar', *Sun* (Australia), 30 Apr 1988; 'Doctors enticed to prescribe anti-diarrhoea pill' (press release), Australian Consumers' Association, Sydney, Apr 1988; Margo, J., 'Medicine men bewitch doctors', *Sydney Morning Herald*, 14 Jan 1989.
3. Chilnick, L.D. (ed.), *The Pill Book*, New York, Bantam Books, (4th edn) 1990, pp46-51
4. Ibid., p473
5. *Physicians' Desk Reference*, op cit at note 1, p2069
6. WHO, *The rational use of drugs in the management of acute diarrhoea in children*, Geneva, WHO, 1990, p12
7. *Drug and Therapeutics Bulletin*, "Prescribing for Acute Diarrhoea", Vol 21, No 26, 30 Dec 1983
8. *Medical Letter*, "Lomotil for diarrhoea in children", No 25, 1975, p104
9. WHO, *The treatment and prevention of acute diarrhoea: Practical guidelines*, Geneva, WHO, (2nd edn) 1989, p4
10. Medawar, C. and Freese, B., *Drug Diplomacy*, London, Social Audit, 1982
11. ABPI, *ABPI Data Sheet Compendium 1988-89*, London, Datapharm Publications, 1988, p577
    BMA and the Royal Pharmaceutical Society of Great Britain, *British National Formulary*, London, BMA and The Pharmaceutical Press, No 21, March 1991, p38
12. Parish, P., *Medicines: a guide for everybody*, London, Penguin (6th edn, revised), 1989, p144
13. Jackson, D.M. and Soothill, R., *Is the Medicine Making You Ill?*, North Ryde (Australia), Angus & Robertson, 1989, pp143-4
14. Chilnick, L.D., op cit, p473
15. Lappé, M., *When Antibiotics Fail*, Berkeley, North Atlantic Books, 1986, p154
16. WHO, 1990, op cit, pp8-11
17. The advertisement was in the October 1990 edition of the *Philippine Index of Medical Specialities*, p25. The study was: Lustman, F., et al, "Diphenocylate hydrochloride (Lomotil) in the treatment of acute diarrhoea", *British Journal of Clinical Practice*, Vol 41, No 2, Mar 1987, p648.
18. WHO, 1990, op cit, p8
19. Ibid., p7
20. Parish, P., op cit, p144
21. Henry, J. (ed.), *The British Medical Association Guide to Medicines & Drugs*, London, Dorling Kindersley, (2nd edn) 1991, p253
    Chilnick, L.D., op cit, p474
    Griffith, H.W., *Complete Guide to Prescription & Non-prescription Drugs*, Los Angeles, The Body Press, (7th edn) 1990, p365
    Reynolds, J.E.F. (ed.), *Martindale: The Extra Pharmacopoeia*, London, The Pharmaceutical Press, (29th edn) 1989, p1088
    Physicians' Desk Reference, op cit, p2069
22. ABPI, op cit, p577
    Griffith, H.W., op cit, p365
    Physicians' Desk Reference, op cit, p2069
23. Henry, J., op cit, p253
    Lappé, M., op cit, p154
    Griffith, H.W., op cit, p365
    Physicians' Desk Reference, op cit, p2069
24. ABPI, op cit at, p577
    Henry, J., op cit, p253
25. Griffith, H.W., op cit, p365
26. Jackson, D.M. and Soothill, R., *Is the Medicine Making You Ill?*, North Ryde (Australia), Angus & Robertson, 1989, pp143-4
27. WHO, 1990, op cit, p7
28. Griffith, H.W., op cit, p365
29. *Physicians' Desk Reference*, op cit, p2069
30. Griffith, H.W., op cit, p365
    Reynolds, J.E.F., op cit, p1087
31. AMA, *Drug Evaluations*, Philadelphia, W.B. Saunders Co., (6th edn) 1986, p965
32. *Physicians' Desk Reference*, op cit, p2070
    Reynolds, J.E.F., op cit, p1087
33. AMA, op cit, p965

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2E. Loperamide

Not for children

In June 1990, executives from the US-based Johnson & Johnson company gathered in the chairman's office in New Jersey to watch a video tape of a documentary made by Britain's Yorkshire Television. The atmosphere in the office was one of "shock" and "stunned silence". As Frank Barker, the corporate vice president for public affairs, said, "You don't see many programmes where you actually see a child die on camera".[1]

The shock was all the more intense because the programme was about the death of infants in Pakistan who had been taking Imodium (loperamide) drops as a treatment for diarrhoea. Imodium, the world's leading antidiarrhoeal drug,[2] is manufactured by Janssen, a subsidiary of Johnson & Johnson.

The drug acts on the muscles of the intestine and slows down movement of the gut contents. However, in very young infants, loperamide can cause paralysis of the intestinal muscle. The result, as was the case in Pakistan, can be death.

This had been observed as long ago as 1980,[3] and standard advice was that loperamide should not be used to treat children under two years of age. In some countries, such as the UK, the age limit was four, while in Australia, loperamide was contraindicated in children under 12 years of age.[4]

However, paediatric formulations (drops or syrup) of loperamide continued to be made by Janssen and other manufacturers. During two months in late 1989, the paediatric department of a teaching hospital in Multan, Pakistan recorded 19 cases of infants who had severe abdominal swelling and intestinal paralysis as a result of having taken loperamide drops produced by Janssen. Eighteen of the children were under seven months of age; the other was two years old. Six of the children died in hospital, four were taken home seriously ill, presumably to die at home, and nine recovered. Two doctors at the hospital wrote to Janssen asking for Imodium drops to be withdrawn from the market. When they received no response, they wrote to *The Lancet* in February 1990, in the hopes that such action would persuade "the manufacturers to withdraw Imodium from Pakistan before it kills any more children".[5]

Janssen responded quickly. The company asked one of the doctors, Dr T.I. Bhutta, for further information about the deaths. A statement was also issued which said that it would be "premature" to take any action until all the details were clear; that all prescribing information for Imodium clearly stated that it should not be used in children under 12 months of age; and that the drops were meant to be on prescription only and used only under medical supervision.[6]

- **Generic name:** loperamide hydrochloride
- **Some brand names:** Imodium, Arret, Imosec (Janssen); Loperium (Remedica); Vacontil (Medochemie); Lopemid (Gentili)
- **Indications from authoritative sources:** *symptomatic* relief of non-infective acute diarrhoea as a secondary measure *after* initiation of rehydration therapy; non-routine use for *symptomatic* relief of some chronic diarrhoeas
- **Essential drug?:** Not on WHO's Essential Drug List
- **Contraindications from authoritative sources:** routine use in ulcerative colitis and Crohn's disease;[7] known hypersensitivity;[8] prolonged use;[9] travellers' diarrhoea;[10] bacterial or parasitic infection of the bowel wall when significant fever or dysentery is present;[11] diarrhoea caused by antibiotic treatment[12]
- **Use in pregnancy:** safety in pregnancy not established[13]
- **Breastfeeding:** should be avoided by breastfeeding women[14]
- **Use in children:** *not* recommended for acute diarrhoeas in young children;[15] not recommended for children under 12 years of age[16]
- **Elderly:** use with caution[17]
- **Special precautions:** use with caution where constipation should be avoided and in liver disorders;[18] discontinue use in acute diarrhoea if no clinical improvement is observed after 48 hours[19]
- **Adverse reactions:** generally rare: abdominal cramps,[20] rash,[21] toxic megacolon,[22] intestinal obstruction,[23] perforation of bowel wall in acute infective diarrhoea[24]

By March of 1990, the situation in Pakistan was confused. Janssen said that it "voluntarily withdrew" Imodium drops from the market in Pakistan,[25] and worldwide;[26] the Pakistan Federal Ministry of Health claimed that it had banned Imodium drops and deregistered all other paediatric preparations containing loperamide;[27] Dr Bhutta wrote again to Janssen telling the company of more children arriving at the hospital with Imodium poisoning and calling for action.[28] In May, the film crew from Yorkshire Television was able to find Imodium drops on sale in six out of 10 pharmacies visited.[29]

By the end of June 1990, Robert Gussin, Johnson & Johnson's corporate vice president for science and technology, said in a letter to *The Lancet* that the company was doing its "utmost" to withdraw the oral drops formulation from Pakistan. He added, "We have also withdrawn the drops in other developing countries and have halted sale worldwide. We are also voluntarily withdrawing Imodium syrup in countries where the World Health Organization has a programme for control of diarrhoeal disease."[30]

Robert Gussin concluded the letter by saying that "the safety and efficacy of Imodium used properly is not at issue". His enthusiasm for the drug is not shared by independent experts around the world.

Loperamide is "not generally recommended" for the treatment of acute infectious diarrhoea "because it may delay the expulsion of harmful substances from the bowel".[31] A careful review by the WHO found little evidence of usefulness of the drug in the treatment of acute diarrhoea in children.[32] Coupled with possible adverse effects which "may be severe when therapy is poorly supervised", this led the WHO to conclude that "loperamide has no place in the routine management of diarrhoea in children" and that there was "no rationale for the production and sale of liquid or syrup formulations for paediatric use". As with many other antidiarrhoeal products on the market, the use of loperamide detracts attention from appropriate management, which includes rehydration and feeding of the patient.

[See also sections on: *Antidiarrhoeals*, *Antibiotics*, *Antidiarrhoeals containing antibiotics*, *Hydroxyquinolines* and *Diphenoxylate*.]

Recommendations for action

1. All products containing loperamide should be contraindicated in children. All paediatric formulations (syrups, drops, etc.) should be banned.
2. All product information and advertising for products containing loperamide should contain a warning that:
   a) oral rehydration therapy is the first-line treatment in most diarrhoeas;
   b) the product should be avoided in acute diarrhoea;
   c) the product should be avoided in pregnant and lactating women, in the elderly, in those with liver dysfunctions and in patients for whom constipation should be avoided;
   d) the product should not be used as routine treatment in inflammatory bowel disease.
3. National regulatory authorities may wish to ban the use of this product as non-essential in the treatment of diarrhoea. At the very least, the production or sale of liquid or syrup formulations for paediatric use should be banned.

Notes and references:

1. Scanlon, C., "Unsafe drugs find buyers abroad", *Detroit Free Press*, 20 May 1991, p4a
2. In Kenya in 1989, for example, Imodium was reported as being prescribed for 40% of children with diarrhoea (see: Anon., "Misuse of antidiarrhoeal medicines", *Lancet*, 21 Oct 1989, p995; Anon., "Antidiarrhoeals again under attack", *Scrip*, 1457, 20 Oct 1989, p29). In the UK, Janssen's two brands of loperamide, Imodium and Arret, account for half the antidiarrhoeal market (see: Anon., "Janssen's ORT product, Rapolyte, introduced in UK", *Scrip*, 1606, 10 Apr 1991, p24).
3. See data cited in: WHO, *The rational use of drugs in the management of acute diarrhoea in children*, Geneva, WHO, 1990, p19
4. Dukes, M.N.G. and Lunde, I., "Review of restrictive actions under the Australian drug regulatory system", *Medical Journal of Australia*, 1, 1982, pp412-16 (cited in letter from MaLAM to Janssen, July 1990)
5. Bhutta, T.I. and Tahir, K.I., "Loperamide poisoning in children", *Lancet*, 10 Feb 1990, p363
6. Anon., "Janssen on loperamide ADRs", *Scrip*, 1491, 23 Feb 1990, p29
7. AMA, *Drug Evaluations*, Philadelphia, W.B. Saunders Co., (6th edn) 1986, p965
8. *Physicians' Desk Reference*, Oradell, NJ, Medical Economics Company, 44th edn, 1990, p1083
9. AMA, op cit, p963
10. Po, A.L.W., *Non-Prescription Drugs*, Oxford, Blackwell Scientific, (2nd edn) 1990, p217
    Chilnick, L.D. (ed.), *The Pill Book*, New York, Bantam Books, (4th edn) 1990, p476
11. AMA, op cit, p966
12. Griffith, H.W., *Complete Guide to Prescription & Non-Prescription Drugs*, Los Angeles, The Body Press, (7th edn) 1990, p573
13. Henry, J. (ed.), *The British Medical Association Guide to Medicines & Drugs*, London, Dorling Kindersley, (2nd edn) 1991, p303
14. Black, G.J. (ed.), *Physician's 1990 Drug Handbook*, Springhouse, PA, Springhouse Corporation, 1990, p575
15. BMA and the Royal Pharmaceutical Society of Great Britain, *British National Formulary*, London, BMA and The Pharmaceutical Press, No 22, Sep 1991, p37
16. Chilnick, L.D., op cit, p477
    The Australian Drug Evaluation Committee also contraindicates loperamide for children under 12 years of age. See: Dukes, M.N.G. and Lunde, I., op cit at note 4.
17. Henry, J., op cit, p303
18. AMA, op cit, p966
19. *Physicians' Desk Reference*, op cit, p1083
20. Gilman, A.G., Rall, T.W., Nies, A.S., and Taylor, P., *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, New York, Pergamon Press, (8th edn) 1990, p508
21. BMA, op cit, p37
22. Reynolds, J.E.F. (ed.), *Martindale: The Extra Pharmacopoeia*, London, The Pharmaceutical Press, (29th edn) 1989, p1094
23. Po, A.L.W., op cit, p32
24. AMA, op cit
25. Advertisement: "Clarification: Imodium Drops", *Dawn* (newspaper in Karachi), 9 Jun 1990
26. Anon., "Janssen acts on Imodium in Pakistan", *Scrip*, 1525, 22 Jun 1990, p10
27. Anon., "Health Ministry's notice", *Dawn*, 13 Jun 1990
28. Bhutta, T.I., "Anti-motility drugs for infants", *Lancet*, 4 Aug 1990, p314
29. Anon., "Loperamide poisoning in children", *Lancet*, 9 Jun 1990, p1394
30. Gussin, R.Z., "Withdrawal of loperamide drops", *Lancet*, 30 Jun 1990, pp1603-4
31. Henry, J., op cit, p303
32. WHO, 1990, op cit, p20

Chetley, A. *Problem Drugs*, Amsterdam,
Health Action International, 1993

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3A. Antibiotics

The antibiotic crisis

In September 1989, more than 500 cases of typhoid were reported from Shrirampur in Maharashtra, India. In 83% of the cases, the bacteria causing the typhoid were resistant to chloramphenicol, the life-saving drug that has been the mainstay in the treatment of typhoid in India. Almost half the patients were children. Twelve deaths were reported, three of these were children. At the national conference of the Indian Academy of Paediatrics in June 1990, similar reports from all over the country were heard. Also heard was the reminder that, for many years, pharmaceutical companies in India had been promoting chloramphenicol and streptomycin combination products for the treatment of acute diarrhoea. The resistance to chloramphenicol that developed as a result of this inappropriate use of the drug was claimed to be responsible for the typhoid deaths.[1]

When antibiotics were first developed, they were seen as "magic bullets" that would radically change the treatment of infectious disease. Now, however, experts are worried that the golden age of antibiotics is over.

> "We may look back at the antibiotic era as just a passing phase in the history of medicine, an era in which a great natural resource was squandered and where the bugs proved smarter than the scientist."[2]

> "It is not clear how long our currently available agents will be useful.... in select settings (particularly hospitals) we are left with few, if any, alternatives."[3]

> "The continual introduction of new antimicrobial agents, many of which are no more than minor chemical modifications, has generated confusion amongst prescribers."[4]

A key reason for the baffling array of so many antibiotics is described by one professor of medicine and pharmacology as "the rapid development of bacterial resistance to every compound that has reached general use".[5]

Antibiotic resistance

According to an international task force studying antibiotic resistance, although antibiotics have saved and improved more lives than any other class of medicines, their use "has set in motion the biggest intervention in population genetics seen to date on this planet. The effects of that intervention are seen in the distributions of antibiotic-resistance genes throughout the world's bacterial populations."[6] This change, although invisible to the naked eye, has had as profound an effect on human health as the antibiotics

How antibiotics work

Antibiotics are usually described as being either bactericidal (they kill bacteria) or bacteriostatic (they slow the growth of bacteria to allow the immune system to destroy the bacteria). For example, the beta-lactam antibiotics are bactericidal because they inhibit the synthesis of bacterial cell walls. Without the cell wall, the bacteria die. Other antibiotics interfere with the chemical processes within the cell, which in turn leads to the death of the bacteria.

The newest type of antibiotics, the quinolones, causes the DNA of the bacteria to uncoil by interfering with an enzyme within the bacteria which ensures that the long strands of DNA can fit inside a small bacterial cell. The result is that the bacteria cannot divide or produce the enzymes they need to carry out normal activities, and they subsequently die.

themselves.[7] One researcher notes that "resistance to antimicrobial agents has become a global problem with a major impact on health care in developed and developing countries".[8]

Some bacteria are naturally resistant to certain antibiotics, but often resistance is acquired. Bacteria become resistant by incorporating a "resistance factor" into their genes to render the antibiotic ineffective. This can pass quickly to other bacteria, carried on small pieces of genetic material called plasmids. The resistant genes can also sometimes be packaged in DNA units called transposons that allow them to jump from one DNA site to another. Multiple resistance, where bacteria are resistant to several antibiotics, can also be transferred from one species to another.[9] The mechanisms of resistance may include: changes occurring within the cell of the bacteria to affect the receptivity to the antibiotic; changes to the cell wall which make it more difficult for the antibiotic to attack; improvement in speed with which the antibiotic is absorbed into or discharged from the cell, thus limiting the time the antibiotic has to work and its effective concentration within the cell; or the production of an enzyme which renders the antibiotic ineffective.[10] Although initially encountered only in urban hospitals, resistant bacteria are now being detected everywhere. They can spread between neighbouring and even distant countries; micro-organisms do not recognise frontiers. "One's bacteria are not solely one's own. Rather, they are shed, excreted, and otherwise spread into the environment, where they become part of a common pool."[11] This rapid spread means that increasing numbers of people no longer respond to antibiotics that were previously effective.

Increased use of any antibiotic "inevitably" results in an increase in resistant bacteria.[12] For example, the likelihood of finding strains of ampicillin-resistant *Haemophilus influenzae* increases in children who previously have received antibiotics.[13] However, resistance to an antibiotic can and does exist in people without prior exposure to the antibiotic in question.[14]

A study by the World Health Organization's (WHO) Programme for Appropriate Health Care Technology (ATH) has shown a correlation between the occurrence of multiresistant bacteria and antibiotic consumption patterns. The study collected data on resistance rates, national consumption, and the distribution of aminoglycoside consumption between hospital and non-hospital outlets in 12 countries. A second study has been commissioned to look at the use of antibiotics in the treatment of tonsillitis, which WHO/ATH claims is inappropriate in at least 50% of all cases. The original study concluded: "the increased frequency and spread of resistant bacterial strains is a consequence of the inappropriate use of antibiotics in outpatient as well as inpatient care.

Major classes of antibiotics

Penicillins
includes drugs such as: amoxycillin, ampicillin, ampicillin with sulbactam, benzylpenicillin, cloxacillin, co-amoxiclav (amoxycillin with clavulanic acid), flucloxacillin, methicillin, oxacillin, phenoxymethylpenicillin

Cephalosporins
cefaclor, cefadroxil, cefixime, cefoperazone, cefotaxime, cefoxitin, cefpirome, cefsulodin, ceftazidime, ceftizoxime, ceftriaxone, cefuroxime, cephalexin, cephalothin, cephamandole, cephazolin, cephradine

The penicillins and cephalosporins – together with monobactam and carbapenem antibiotics – are collectively known as beta-lactam antibiotics. Other beta-lactam antibiotics include: aztreonam, imipenem (which is usually administered in combination with cilastatin)

Aminoglycosides
amikacin, gentamicin, kanamycin, neomycin, netilmicin, streptomycin, tobramycin

Macrolides
azithromycin, clarithromycin, erythromycin, josamycin, roxithromycin

Lincosamides
clindamycin, lincomycin

Tetracyclines
doxycycline, minocycline, oxytetracycline, tetracycline

Quinolones
nalidixic acid, ciprofloxacin, enoxacin, fleroxacin, norfloxacin, ofloxacin, pefloxacin, temafloxacin (withdrawn in 1992)

Others
chloramphenicol, co-trimoxazole (trimethoprim and sulfamethoxazole), mupirocin, teicoplanin, vancomycin

Note: Technically, antibiotics are only those substances produced by microbes. Thus, antibacterials or antimicrobials such as the sulphonamides, the quinolones, and trimethoprim are not strictly antibiotics. However, they are included in the discussion in this section.

Therefore, a concentrated and determined action for the establishment of national and global policies on the appropriate utilisation of antibiotics is urgently needed."[15]

A possible reason for the dramatic increase in *Streptococcus pneumoniae* strains resistant to penicillin in Hungary over a 15-year period from 1975 to 1989 was "the uncontrolled, injudicious, and frequent administration of penicillin and its derivatives." Researchers who were studying this phenomenon called for an antibiotic policy that limited the use of antimicrobials as one of the more effective ways to prevent the further spread of resistant strains.[16]

Researchers examining the problems of resistance among *S. pneumoniae* strains in Spain concluded that two essential measures seemed necessary to improve the situation: "exhaustive surveillance of resistance and strict control of antibiotic use".[17]

A meeting of a WHO working group in the Western Pacific region found that bacterial resistance was a problem in Australia, Brunei, China, Hong Kong, Japan, Malaysia, New Zealand, Papua New Guinea, the Philippines, South Korea, Singapore and Vietnam. It has called for an information network in the region to monitor the situation.[18]

Resistance costs lives and money

The inability to treat infections with the usual antibiotic of choice (or any other drug) can be disastrous. Gonorrhoea, dysentery, pneumonia, meningitis, and deadly hospital infections have all been taking their toll.

Gonorrhoea is now established as a leading worldwide public health problem. Within developing countries, gonorrhoea caused by resistant strains of *Neisseria gonorrhoeae* has become hyperendemic.[19] In industrialised countries too, resistant strains are on the increase.[20]

Resistance to commonly used antibiotics for the treatment of dysentery has become more prevalent. Generally, the majority of *Shigella* isolates found in different countries are now resistant to tetracycline and sulphonamides. Increasing resistance to both ampicillin and co-trimoxazole has been reported in Asia, Africa and North America and some resistance to nalidixic acid has been reported. In communities where nalidixic acid is commonly used, widespread resistance is expected to develop quickly.[21]

Resistance of *Haemophilus influenzae* to common antibiotics is particularly worrying for children's health. Infections caused by *H. influenzae* type b (Hib) represent more than 90% of invasive diseases in young children. These include meningitis and

Types of bacteria

Most bacteria consist of single cells, each with a protective wall. They are classified and identified according to the properties of their cell walls. This is usually indicated by a staining process developed by H.C.J. Gram in 1884. Gram-positive bacteria are those which readily absorb the initial dye, while gram-negative bacteria are those which do not.

Bacteria can also be classified according to their shape. Cocci are round, bacilli are rod-shaped and spirochaetes are coiled. If the cocci are arranged in a straight line, they are called streptococci; if they are found in clumps, they are called staphylococci. Diplococci occur in pairs.

Another classification divides bacteria into those which require free oxygen in the air, aerobes, and those which do not, anaerobes. Anaerobic and aerobic bacteria play a common role in many infections. Both anaerobes and aerobes can be either gram-positive or gram-negative. Anaerobes are particularly to be found in the head and neck, the upper respiratory tract, the lower gastrointestinal tract, the genital tract and occasionally in skin and soft tissue. Their role in infections is not always recognised, in part because of the difficulty in confirming a diagnosis, due to the need to collect and transport samples in an "air-free" container to avoid contamination with aerobic bacteria. Several of the very "broad spectrum" antibiotics introduced in recent years have very poor activity against anaerobic pathogens, an important consideration when such agents are proposed as monotherapy for mixed infections.

Some bacteria, particularly those that live in the human gut, are essential for human life. For example, some of them synthesise vitamins. Indiscriminate use of broad-spectrum antibiotics may destroy these useful bacteria.

Sources: Styrt, B. and Grobach, S.L., "Recent developments in the understanding of the pathogenesis and treatment of anaerobic infections", parts one and two, *New England Journal of Medicine*, Vol 321, No 4, 27 Jul 1989, pp240-6 and Vol 321, No 5, 3 Aug 1989, pp298-302

pneumonia.[22] In most developing countries, bacterial meningitis is associated with a high fatality rate – up to 70% of cases in some settings.[23]

Staphylococcus aureus is a particular menace in hospitals, where it can infect and kill surgical patients who have had skin grafts or organ tranplants, and can also cause pneumonia, meningitis, and septicaemia, as well as less serious infections such as boils and abcesses. This organism has been described as "one of the most versatile of human pathogens"[24] because it can acquire resistance to virtually all available antibiotics. One study of 106 strains of methicillin-resistant *S. aureus* (MRSA) from 21 countries found that more than 90% were also resistant to gentamicin, tobramycin, netilmicin, amikacin, streptomycin, and erythromycin. Resistance to the quinolone, ciprofloxacin, was found in 17%. This was described as "disconcerting", because of the antibiotic's novel structure and its recent entry into clinical use.[25]

One expert notes that bacterial resistance to antibiotics is "a major obstacle to the treatment of infectious diseases, leading not only to treatment failures but also to increased costs."[26] The cost of antibiotic resistance in the USA has been estimated at more than $100 million a year.[27] There is another cost as well: the human one. Infections caused by resistant bacteria are more likely to cause prolonged illness, frequent and prolonged hospitalisation and a higher death rate.[28]

The pharmaceutical industry can hardly claim that it is unaware of the problem of resistance. In 1988 alone, *Scrip*, a journal which reports on developments in the pharmaceutical industry, published eight articles about antibiotic resistance.[29] Most articles in medical journals about antibiotics at least mention the question of resistance. Table 3A-1 summarises some of the findings.

Use and misuse in industrialised countries

The *use* of antibiotics is widespread in industrialised countries. In Sweden, antibiotic prescribing increased by 12% between 1987 and 1988.[30] In the UK, one in every six prescriptions is for antibiotics.[31] In Australia, antibiotics accounted for 17-20% of all drugs prescribed,[32] and in 1986, amoxycillin was the most widely prescribed of all drugs.[33] In 1988, the most often prescribed drug in the USA was a brand of amoxycillin, Amoxil, produced by Beecham.[34] In the USA in 1986, about 35% of the 57.8 million prescriptions for children under the age of three were for anti-infective agents.[35]

Much evidence indicates that antimicrobials are often *misused*.[36] The Health and Public Policy Committee of the American College of Physicians says that

Table 3A-1
Examples of reports of antibiotic resistance

Antibiotic	Bacteria	% of resistance	Year of study	Location of study
amikacin	Ps. aeruginosa	12	1990	Italy[20]
aminoglycosides	Ps. aeruginosa	0.5	n.a.	Sweden[2]
aminoglycosides	Ps. aeruginosa	60	n.a.	France[2]
amoxicillin	E. coli	60	1985-7	Hong Kong[22]
amoxicillin	H. influenzae	24	1987-9	Atlanta, USA[13]
ampicillin	H. influenzae	12-18	n.a.	UK[9]
ampicillin	H. influenzae	20-40	n.a.	USA[10]
ampicillin	H. influenzae	24	1987-9	Atlanta, USA[13]
ampicillin	H. influenzae	31	1990	Spain[15]
ampicillin	H. influenzae	12-27	1990	Belgium[15]
ampicillin	H. influenzae	11-13	1990	France[15]
ampicillin	H. influenzae	6	1990	Switzerland[15]
ampicillin	Shigella	96	1987	Sudan[6]
ampicillin	Shigella	43	1988	Turkey[7]
ampicillin	Shigella	33-100	1988	Nigeria[21]
ampicillin	E. coli	60	1985-7	Hong Kong[22]
chloramphenicol	Shigella	72	1987	Sudan[6]
chloramphenicol	Shigella	37	1988	Turkey[7]
chloramphenicol	Shigella	25-100	1988	Nigeria[21]
chloramphenicol	S. pneumoniae	39	1986-9	Pakistan[8]
chloramphenicol	typhoid	83	1989	India[1]
ciprofloxacin	S. aureus	91	1990	Atlanta, USA[12]
co-amoxiclav	E. coli	20	1985-7	Hong Kong[22]
co-trimoxazole	H. influenzae	12	1987-9	Boston, USA[17]
co-trimoxazole	Shigella	53	1988	Turkey[7]
co trimoxazole	Shigella	50-100	1988	Nigeria[21]
co-trimoxazole	S. pneumoniae	31	1986-9	Pakistan[8]
co-trimoxazole	E. coli	32-35	1983-4	Finland[23]
erythromycin	enterococci	90	1990	Boston, USA[24]
gentamicin	enterococci	13-55	1990	USA[16]
gentamicin	Ps. aeruginosa	31	1990	Italy[20]
nalidixic acid	Shigella	23	1988	Turkey[7]
nalidixic acid	Shigella	85	1987	Bangladesh[19]
netilmicin	Ps. aeruginosa	13	1990	Italy[20]
pefloxacin	S. aureus	6	1985	France[11]
penicillin	N. gonorrhoeae	14	1988	Holland[5]
penicillin	N. gonorrhoeae	20	1986	Amsterdam[5]
penicillin	N. gonorrhoeae	20-30	n.a.	New York, USA[4]
penicillin	N. gonorrhoeae	17	1989	USA[14]
penicillin	S. pneumoniae	40	1988	Spain[18]
penicillins & cephalosporins	N. gonorrhoeae	30-40	n.a.	Asia[3]
penicillins & cephalosporins	N. gonorrhoeae	25-50	n.a.	Africa[3]
streptomycin	Shigella	80	1988	Turkey[7]
streptomycin	Shigella	84	1987	Sudan[6]
streptomycin	Shigella	50-100	1988	Nigeria[21]
sulphonamides	Shigella	90	1987	Sudan[6]
tetracycline	N. gonorrhoeae	17	1989	USA[14]
tetracycline	Shigella	92	1987	Sudan[6]
tetracycline	Shigella	40	1988	Turkey[7]
tobramycin	Ps. aeruginosa	11	1990	Italy[20]
trimethoprim	Shigella	77	1987	Sudan[6]
trimethoprim	E. coli	34-40	1983-4	Finland[23]

perhaps as many as 64% of antibiotic prescriptions in hospitals are unnecessary or include inappropriate dosages.[37] Overall, the result of several studies conducted in the USA suggests that 40 to 60% of all antibiotics are misprescribed.[38] Antibiotics are often wrongly prescribed for minor infections[39] or to treat the common cold,[40] which is caused by a virus. A survey of physicians in the USA showed that 60% prescribed antibiotics for treating colds.[41] In the UK, about one-third of all hospital patients receive at least one antibiotic, and in about half these cases, the antibiotic is inappropriately prescribed.[42] A Canadian study found that at least one-third and perhaps as much as one half of antibiotics were inappropriately prescribed in hospitals.[43] The vast sales of antibiotics in Italy in 1989 ($1.2 billion) prompted the Italian Health Ministry to comment that this enormous consumption "unfortunately confirms the indiscriminate and often unjustified use of antibiotic therapy for the treatment of frequently benign infections".[44] In Australia, more than Aus $3 million a year could be saved if doctors prescribed according to peer-consensus recommendations for the treatment of tonsillitis and urinary tract infection. Microbiologist Dr Ken Harvey says, "the current situation would appear to be the result of leaving continuing education concerning therapeutics primarily in the hands of the pharmaceutical industry".[45]

Inappropriate use of restricted antibiotics was found in 22 out of 73 cases surveyed in a recent study in New Zealand, representing an excess cost of NZ $3,282 (US $2,202). The most common fault was prescribing antibiotics as prophylaxis for too long a period. Other studies have shown that 31 to 66% of antibiotics are used inappropriately. According to Professor John Smith of Otago University, antibiotic prescribing guidelines should be introduced to help doctors cope with "the continuing avalanche" of new and more expensive antibiotics.[46]

In the USA, "the need for limiting the number of antibiotics that a physician will use in routine practice" is evident from the list of 92 antibacterial drugs in the 1990 edition of the *Physician's Desk Reference*.[47] The WHO Essential Drugs List contains 16 antibiotics.[48]

The misuse of antibiotics also increases the dangers of side effects. These may be specific (for example, chloramphenicol can damage the bone marrow; neomycin may damage the kidneys), or due to hypersensitivity or allergic reactions. Furthermore, a disturbance in the balance of the body's microorganisms by antibiotics can lead to superinfections or overgrowth of yeasts, fungi and bacteria. These are usually minor but may become serious or even fatal. They are difficult to treat and are more likely to occur with broad-spectrum antibiotics (those effective against a wide variety of bacteria), in children under three years of age, or in the elderly.[49] Most

Table 3A-1

Sources:

1. Anon., "Who is responsible for these unnecessary typhoid deaths?", *ACASH News*, Dec 1990, p1
2. Anon., 'WHO/ATH on the misuse of antibiotics', *Scrip*, 1272/3, 8/13 Jan 1988, p26; O'Neill, P. and McIntosh, S., 'Bacteria resistant to antibiotics spread concern', *New Scientist*, 27 Aug 1987, p16
3. O'Brien, T.F., et al, "Resistance of bacteria to antibacterial agents: report of Task Force 2", *Reviews of Infectious Diseases*, Vol 9 (Suppl. 3), May Jun 1987, ppS244-60
4. Neu, H.C., "Antimicrobial agents: the old and the new", *American Journal of Infection Control*, Vol 17, No 5, Oct 1989, pp276-85
5. van Klingeren, B., Dessens-Kroon, M., Verheuvel, M., "Increased tetracycline resistance in gonococci in The Netherlands", *Lancet*, 25 Nov 1989, p1278
6. Shears, P., "The Khartoum floods and diarrhoeal diseases", *Lancet*, 27 Aug 1988, p517
7. Ceyhan, M., Dilmen, U., Korten, V., et al, "Shigella diarrhoea and treatment", *Lancet*, 2 July 1988, pp45-6
8. Mastro, T.D., Ghafoor, A., et al, "Antimicrobial resistance of pneumococci in children with acute lower respiratory tract infection in Pakistan", *Lancet*, 19 Jan 1991, Vol 337, No 8734, pp156-9
9. Chapman, S.T. and Walsh, T.H., "Which Antibiotic for Surgical Nosocomial Infection?" *British Journal of Clinical Practice*, Vol 45, No 2, Summer 1991, pp141-4
10. Vallejo, J.G., Kaplan, S.L. and Mason, E.O., "Treatment of meningitis and other infections due to ampicillin-resistant *Haemophilus influenzae* type b in children", *Reviews of Infectious Diseases*, Vol 13, Mar Apr 1991, pp197-200
11. Aboukasm, A.G., Buu-Hoi, A.Y., et al, "Epidemiological study of *Staphylococcus aureus* resistance to new quinolones in a university hospital", *Journal of Hospital Infection*, Vol 17, 1991, pp25-33
12. Blumberg, H.M., Carroll, D.J. and Wachsmuth, I.K., "Rapid development of ciprofloxacin resistance in methicillin susceptible and -resistant *Staphylococcus aureus*", *Journal of Infectious Diseases*, Vol 163, Jun 1991, pp1279-85
13. Jacobs Jr., N.F. and Jerris, R.C., "*Haemophilus influenzae* resistance in a community hospital", *Southern Medical Journal*, Vol 84, No 6, Jun 1991, pp730-2
14. Handsfield, H.H., McCormack, W.M., et al, "A comparison of single-dose cefixime with ceftriaxone as treatment for uncomplicated gonorrhea", *New England Journal of Medicine*, Vol 325, No 19, 7 Nov 1991, pp1337-41
15. Cullmann, W. and Then, R.L., "Cefetamet: its *in vitro* activity and interaction with beta-lactamases and penicillin-binding proteins", *Drug Investigation*, Vol 3, No 5, 1991, pp299-307
16. Boulanger, J.M., Ford-Jones, E.L. and Matlow, A.G., "Enterococcal bacteremia in a pediatric institution: a four-year review", *Reviews of Infectious Diseases*, Vol 13, Sep-Oct 1991, pp847-56
17. Pelton, S.I., Teele, D.W., et al, "Trimethoprim/sulfamethoxazole-resistant nontypable *Haemophilus influenzae*", *Pediatric Infectious Disease Journal*, Vol 10, No 11, Nov 1991, pp873-4
18. Munoz, R., Coffey, T.J., et al, "Intercontinental spread of a multiresistant clone of serotype 23F *Streptococcus pneumoniae*", *Journal of Infectious Disease*, Vol 164, Aug 1991, pp302-6
19. Munshi, M.H., Haider, K., et al, "Plasmid-mediated resistance to nalidixic acid in *Shigella dysenteriae* type 1", *Lancet*, 22 Aug 1987, pp419-21
20. Toscano, M.A., Minneci, M., et al, "New epidemiological data on resistance to netilmicin and other aminoglycosides", *Journal of Chemotherapy*, Vol 3, No 6, 1991, pp352-6
21. Eko, F.O. and Utsalo, S.J., "Antimicrobial resistance trends of shigellae isolates from Calabar, Nigeria", *Journal of Tropical Medicine and Hygiene*, Vol 94, 1991, pp407-10
22. French, G. and Ling, T., "Amoxycillin/clavulanic acid resistant *Escherichia coli*", *Lancet*, 26 Mar 1988, p704
23. Huovinen, P., Pulkkinen, L., et al, "Emergence of trimethoprim resistance in relation to drug consumption in a Finnish hospital from 1971 through 1984", *Antimicrobial Agents and Chemotherapy*, Vol 29, No 1, Jan 1986, pp73-6
24. Moellering, R.C., "Introduction: Revolutionary changes in the macrolide and azalide antibiotics", *American Journal of Medicine*, Vol 91 (Suppl. 3A), 12 Sep 1991, p3A-2S

classes of antibiotics may have some negative effect on male fertility.[50]

In the USA, a 1988 study found that 2% of 6,546 paediatric admissions to general or specialty paediatric wards (excluding neonates and children with cancer) were prompted by adverse drug reactions. The eight drugs most commonly implicated included three antibiotics: ampicillin, amoxycillin and co-trimoxazole. A 1985 study found that the main antibiotic-related adverse reactions among 4,244 courses of paediatric outpatient drug therapy were gastrointestinal complaints and rashes. The study also noted that 64% of paediatric outpatient prescriptions were for antibiotics.[51]

Misuse in developing countries

The threat of infection in the Third World through poverty, malnutrition, poor sanitation and poor housing conditions means that antibiotics have a potentially important role to play in improving health care. In underdeveloped countries, a large proportion of the drug budget is spent on antibiotics and antiparasitic drugs. Frequently, more money is spent on antibiotics than on any other class of drugs.[52]

However, as in industrialised countries, antibiotics are only effective if they are properly used. The reality is very different. "Most use of antibiotics in developing countries is inappropriate; medications that are available without prescription are used for too short a period, at too low a dose, or without proper indication."[53]

Many antidiarrhoeal preparations containing antibiotics (neomycin, streptomycin, chloramphenicol, sulphonamides) are on the Third World market. According to WHO, "antibiotics are not effective against most organisms that cause diarrhoea. They rarely help and can make some people sicker in the long term. Their indiscriminate use may increase the resistance of some disease-causing organisms to antibiotics. In addition, antibiotics are costly, so money is wasted. Therefore, antibiotics should not be used routinely."[54]

Dr Efraín Margolis, professor of preventive and social medicine, says that in Uruguay one of the causes of the unnecessarily high use of antibiotics is the influence of commercial advertising. Manufacturers' indications tend to exceed the main spectrum of use of a particular antibiotic.[55] Dr Margolis notes the erroneous use of antibiotics in viral infections and points to an "explosive" use of antibiotics during flu epidemics. Also there are many combination antibiotics in Uruguay, despite international recommendations that monosubstances are preferred.

Overprescribing and inappropriate prescribing of antibiotics by physicians are common in the Third World. In Nigeria, for example, one study found that 33% of prescriptions in government and private hospital were inappropriate.[56] In the Middle East, overprescribing is often due to an imprecise diagnosis and lack of confidence on the part of a health worker, combined with a desire to please the patient, according to advisers to WHO's Middle East Regional Office.[57]

Dr Abdulla Assad, director of pharmaceutical services in Kuwait, says the country urgently needs a clear policy on the rational use of antibiotics. He has called for better research on patterns of antibiotic resistance in Kuwait and stricter controls on antibiotic prescribing and dispensing. He says that doctors are currently prescribing antibiotics without knowing whether pathogens are resistant to them and are also prescribing larger quantities than required.[58]

Assuming that diagnosis reveals underlying bacterial infection, "the most effective, least toxic, narrowest spectrum agent available" should be used to "reduce the problems associated with broad-spectrum therapy, viz. selection of resistant micro-organisms and superinfection."[59] However, many people do not see a doctor or get a diagnosis. They simply buy antibiotics without a prescription over the counter. This widespread self-treatment, often with the least effective agent in an incorrect dosage, is considered a major factor in the development of bacterial resistance in developing countries.[60] One study in Nigeria found that all 500 members of the public surveyed and 73% of 500 university students admitted to having used antibiotics at least once for a variety of symptoms before consulting a physician.[61] A survey in pharmacies serving low-income populations in Fortaleza,

Table 3A-2
Antibiotics as a percentage of the total pharmaceutical market in selected countries

Country/Region	Year	Sales of antibiotics as % of total market	Total sales of antibiotics US$ million
Iran	1990	31	–
Middle East	1989	29	71
Indonesia	1989	25	100
Philippines	1989	23	98.9
Mexico	1990	15	300
Argentina	1990	12	177.5

Sources: Iran: *Scrip*, 1550, 19 Sep 1990, p21; Middle East (refers to seven countries: Saudi Arabia, Jordan, the United Arab Emirates, Bahrain, Kuwait, Qatar and Oman): *Scrip*, 1499, 23 Mar 1990, p29; Indonesia: *Scrip*, 1483, 26 Jan 1990, p17; Philippines: *Scrip*, 1485, 2 Feb 1990, p20; Mexico: *Scrip*, 1598, 13 Mar 1991, p22; Argentina: *Scrip*, 1638, 31 Jul 1991, p23

Brazil found that counter staff routinely recommended antibiotics for acute respiratory infections.[62]

Antibiotics in animals

About half of all antibiotics produced in the USA are administered to animals, either to prevent or treat disease, or in feed stock to promote growth.[63] It has long been recognised by farmers that antibiotics can cause healthy animals to put on weight without consuming more food.[64] The commonest growth promoters are tetracyclines – among the most potent drugs for provoking the rise and selection of resistant organisms. In 1985, over 90% of the drugs used in animals in the USA were used without any veterinarian involved. It is common practice for farm workers to buy antibiotics directly from feed stores or other suppliers; veterinarians are called only if problems develop after treating the animals with the antibiotics.[65]

Antibiotics have been extensively but unsuccessfully used in animals to prevent infectious diarrhoea caused by salmonella. The spread of antibiotic-resistant salmonella from animals to humans was noted in 38 outbreaks investigated by the US Centers for Disease Control between 1971 and 1983.[66] The Natural Resources Defense Council said in 1985 that 300 deaths and 270,000 cases of salmonella poisoning each year in the USA could be traced to the use of tetracycline and penicillin as growth stimulants in animals. In the United Kingdom in 1964, there were only 4,500 cases of salmonella food poisoning reported; by 1983, the figure had reached 17,000.[67]

Veterinary drugs are sold and used without much control in Nigeria, which may have created a population of resistant bacteria in the animals. The presence of antibiotic residues in meat, milk and their products poses potential human health hazards. Allergic skin conditions, nausea, vomiting, anaphylactic shock and even death have resulted from the ingestion of residues. Cooking and freezing have minimal effect on residues. Resistance to antibiotics has been detected in food poisoning bacteria such as *Salmonella typhimurium*, *Staphylococcus aureus* and *Clostridium perfringens*. Some epidemiological link has been established between *S. typhimurium* of calves and human food poisoning. Judicious use of antibiotics, public education on the health risks of the indiscriminate use of drugs in livestock production, and hygienic slaughter, will help to reduce bacterial drug resistance in man and animals, according to a researcher at the Department of Veterinary Medicine, University of Nigeria.[68]

Evidence of increasing resistance of *Salmonella* bacteria in poultry to the newer quinolones used to treat salmonellosis in humans was described by four British researchers as "worrying". They said that "thought needs to be given as to whether quinolones, such as enrofloxacin, should be given to animals".[69]

Clinical trials

Susceptibility of bacteria to a particular antibiotic in the laboratory does not necessarily mean that the antibiotic will be effective in clinical practice. For example, in laboratory tests (*in vitro*), *Helicobacter pylori* is sensitive to most antibiotics (penicillin, ampicillin, cephalosporins, macrolides, quinolones, aminoglycosides, tetracyclines, and nitroimidazoles) except vancomycin, trimethoprim and sulphonamides. However, the clinical experience with various antimicrobials has been particularly disappointing, especially when these have been administered alone.[1] Similarly, not all antimicrobials that are active *in vitro* against *Shigella* are effective in practice. Thus, "efficacy of an agent can only be assessed by properly conducted clinical trials".[2]

In the past, efficacy as determined by controlled clinical trials was the single factor that determined the prescribing of antibiotics. However, efficacy is rarely emphasised in currently published clinical trials of new antibiotics simply because analysis of results almost always demonstrates therapeutic equivalence rather than superiority of new compounds as compared to previous standard regimens.[3] The number of patients studied is usually too small to show any difference in efficacy.[4]

One expert has stated that the rapidly expanding field of beta-lactam antibiotics has led to "a steadily increasing flood of papers covering trials which are all too often badly planned and dubiously performed".[5]

Sources:

1. Glupczynski, Y., and Burette, A., "Drug therapy for *Helicobacter pylori* infection: problems and pitfalls", *American Journal of Gastroenterology*, Vol 85, No 12, 1990, pp1545-51
2. Salam, M.A. and Bennish, M.L., "Antimicrobial therapy for shigellosis", *Reviews of Infectious Diseases*, Vol 13, Suppl. 4, Mar-Apr 1991, pS332
3. Steele, R.W. and Kearns, G.L., "Antimicrobial therapy for pediatric patients", *Pediatric Clinics of North America*, Vol 36, No 5, Oct 1989, pp1321-49
4. Bergeron, M.G., "The future of new oral antibiotics including the quinolones", *Canadian Medical Association Journal*, Vol 138, 1 Jan 1988, pp35-42; Smith, G.H., "Oral cephalosporins in perspective", *DICP. The Annals of Pharmacotherapy*, Vol 24, Jan 1990, pp45-51
5. Midtvedt, T., "Penicillins, cephalosporins and tetracyclines", in Dukes, M.N.G. (ed.), *Side Effects of Drugs Annual 9*, Amsterdam, Elsevier, 1985, p230

An enormous market

The global antibiotics market was put at $15.5 billion in 1991,[70] and estimates suggest it will increase to $22 billion by 1993,[71] and a possible $40 billion by the year 2000.[72] In the USA in 1989, more than $1.1 billion was spent on just five new, expensive oral antibiotics: ciprofloxacin (Cipro made by Miles/Bayer), norfloxacin (Noroxin by Merck Sharp and Dohme), amoxycillin/clavulanate (Augmentin by SmithKline Beecham), cefuroxime axetil (Ceftin by Glaxo) and cefaclor (Ceclor by Eli Lilly). The total US antibiotic market is worth some $6 billion a year.[73]

The efforts by drug companies to get a large share of this massive world antibiotics market is a major factor behind the misuse.

> "Since the drug industry is profit oriented, it tries to increase the sales of antibiotics. This occurs either by increasing the volume (which leads to unnecessary prescribing) or increasing the relative proportion of expensive antibiotics, which usually are not drugs of choice. It is therefore questionable whether optimal prescribing of antibiotics can be attained in this context."[74]

The connection between promotion and misuse is clear. In Northern Ireland, for example, there was a dramatic increase in prescribing of pivampicillin in 1987-8 after several years of declining use; the increase corresponded with concerted local promotion by the manufacturer.[75] The largest consumer-governed health maintenance organisation (HMO) in the USA recently placed the quinolone antibiotic ciprofloxacin on its formulary with specific use criteria. The HMO's review group responsible for the formulary was concerned about the potential for inappropriate prescribing "due to the intense marketing of this agent, which may have led physicians to believe it was the most appropriate drug for most infections".[76] One commentator describes this as a typical industry approach in its promotion: "While the boldface ad advocates 'blind' use of their product, the fine print embodies the spirit of conservative practice. This classic double message, i.e., 'use our product without hesitation' and 'use our product only with great caution', is typical of many drug company circulars containing prescribing information."[77]

Between July and December 1988, nine of the 17 breaches of the Australian Pharmaceutical Manufacturers Association (APMA) Code of Conduct concerned antibiotics. An advertisement by Eli Lilly for Keflex (cephalexin) 'implied that Keflex was the first drug of choice for tonsillitis, even though this was negated by a warning in small print at the bottom of the advertisement'. A Wellcome advertisement for Septrin (co-trimoxazole) was termed 'misleading' with regard to its claims about resistance, while a second advertisement failed to include

Figure 3A-1
Share of world antibiotics sales in 1991 (percentages)

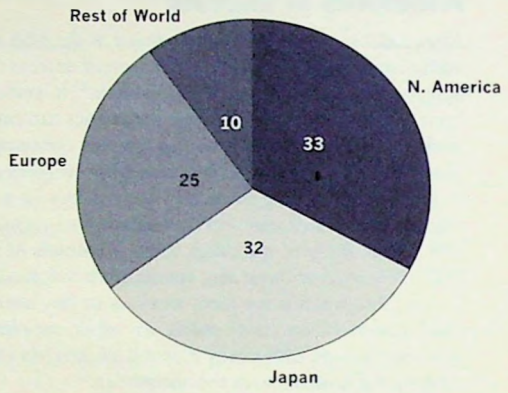


Figure 3A-2
World market share by antibiotic type in 1991 (percentages)

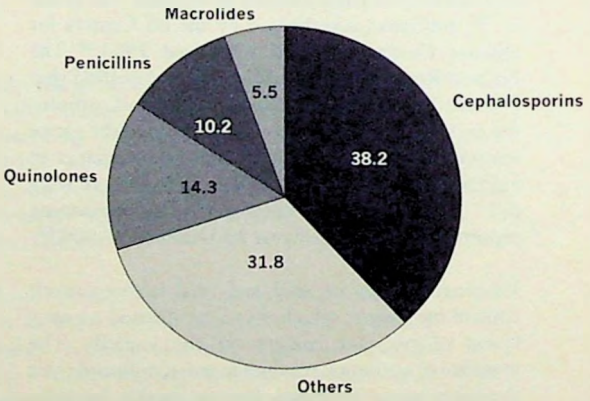
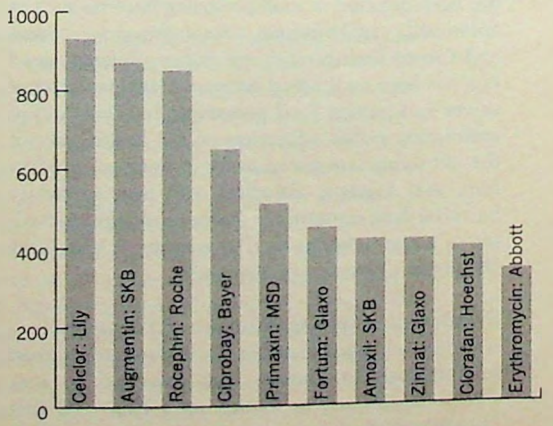


Figure 3A-3
Antibiotic sales 1991 (US$ millions)



Source: Anon. "8% growth for anti-infective market", *Scrip*, No 1791, 2 Feb 1993, p25

or third-line therapy when amoxycillin, penicillin V, or TMP/SMX [co-trimoxazole] have either failed or caused hypersensitivity reactions."[90]

Most independent advice is that they should be used "only for well-defined indications. Excessive use fosters the emergence of resistant organisms and wastes valuable, expensive drugs."[91] Because of this, "limited stocks of these agents, third generation cephalosporins should be kept and their use strictly controlled by adherence to an antibiotic policy."[92]

They are widely used in surgical practice, particularly for surgical prophylaxis.[93] This is despite the advice that "cephalosporins have little role as first-line therapy for surgical nosocomial hospital-acquired infection".[94]

They are "not necessarily the drugs of choice in any pediatric infection", although they provide useful alternative therapies in many situations. For paediatric practice, the general rule is that "more narrow spectrum, less expensive agents should be used".[95]

The AMA echoes those words when talking about the *general* use of cefotaxime, (Claforan), or other third generation cephalosporins.[96] It also makes the point that "additional clinical studies are necessary before specific recommendations about use can be made". Hoechst is less restrained, advising doctors in Thailand to use Claforan "when you have to be right from the start".[97] Claforan was Hoechst's leading drug in 1984 with sales of $223 million, about 10% of the company's total pharmaceutical turnover,[98] and has remained the company's best selling drug with sales of $400 million in 1990,[99] about 8.5% of total pharmaceutical turnover.

A Glaxo advertisement for its brand of ceftazidime, Fortum, in Pakistan in 1990 was dramatic in its appeal: "No time for trial, little room for error. Make no mistake in serious infections... Fortum performs well – right from the start." In the background of the ad was a repeating list of 16 bacteria that the drug was effective against; the repetition of the names, however, created the impression that this antibiotic had a virtually unlimited spectrum of action.[100]

Another Glaxo advertisement in the same publication keeps up the idea of broad coverage and wide usage of its cephalexin antibiotic, Ceporex. In this advertisement, the hands of a baby and an old person are shown linked together, while the headline reads: "From early days, till autumn years, an antibiotic for all seasons, Ceporex".[101] With promotion like this, it is no surprise that statements like "cephalexin undoubtedly is used excessively"[102] appear in the medical literature.

The idea these companies are trying to get across is: don't wait for the results of laboratory sensitivity tests. This type of promotion encourages what has been described as "spiraling empiricism" in medicine. However, as a doctor at the Robert Wood Johnson Medical School in New Jersey, USA points out: "The failure to initiate prompt antibiotic therapy in a febrile but stable immunocompetent patient without identifiable infection is almost never a serious error, even in the presence of occult bacterial infection."[103]

Quinolones

Quinolones (or fluoroquinolones) are among the newest antibiotics to be developed, although the first quinolone to be developed, nalidixic acid, has been available for many years. Nalidixic acid is used in the treatment of some urinary tract infections and in the treatment of *Shigella* dysentery despite its frequent side effects and the ease with which resistance to it develops.[104]

Quinolones accounted for about 15% of the world antibiotics market in 1990.[105] Sales in Europe were $600 million in 1991 according to Frost & Sullivan.[106] Every day, Americans spend $700,000 on ciprofloxacin, but much of this expenditure is inappropriate, according to clinicians in the USA. In 1989, ciprofloxacin was the fourth most commonly prescribed antibiotic in the USA, with more than five million prescriptions filled at a total cost of $248 million. The "astonishing popularity" of ciprofloxacin is

Glaxo ad for cephalexin (Ceporex) in QIMP, Pakistan, 1988-89

a caution about use in the elderly. A booklet produced by Roche entitled *Co-trimoxazole in perspective* was 'assembled carelessly and was misleading', as was an advertisement for Bactrim (co-trimoxazole) and an entire advertising campaign for Bactrim was termed 'unbalanced and misleading by implication and omission'. A Glaxo advertisement for Ceporex (cephalexin) made unsubstantiated claims about efficacy. A Beecham advertisement for Augmentin (amoxycillin) was regarded as 'misleading', while another Beecham advertisement for Floxapen (flucloxacillin) used 'unqualified superlatives'.[78]

Penicillins

Penicillins – probably the most famous antibiotics – include a range of valuable antibiotics which, if used properly, are very effective. Global sales of penicillins in 1988 amounted to $3 billion.[79] Amoxycillin, which is similar to ampicillin, has been gaining in popularity in recent years. Sales of the world's leading brand of amoxycillin, Amoxil, rose from $404 million in 1988 to $436 million in 1990, while sales of the amoxycillin with clavulanate combination, Augmentin, rose from $427 million to $793 million.[80]

Both ampicillin and amoxycillin are widely prescribed for upper and lower respiratory infections, urinary infections (such as cystitis) and other infections. They are often used inappropriately – for the wrong disorder, in the wrong dosage, and for the wrong length of time. Frequently, they are used for disorders which would improve faster on benzylpenicillin or penicillin V.[81]

Promotional material for SmithKline's ampicillin, Eskaycillin, in Bangladesh in 1989, claimed that the antibiotic was "highly successful" in a wide range of infections. It cited studies which it claimed showed a success rate of more than 90% in respiratory tract infections; 100% in cystitis; 88% in typhoid fever; 95% in gonorrhoea; 86% in bacillary dysentery; and 88.4% in bacterial enteritis. Unfortunately, the studies cited were from 1963, 1964, 1964, 1963, 1963 and 1967 respectively – anywhere from 22 to 25 years old. This is some distance from the statement in the Code of Pharmaceutical Marketing Practices of the International Federation of Pharmaceutical Manufacturers Associations (IFPMA) which says that information provided by companies "should be based on an up-to-date evaluation of all the available scientific evidence".[82]

None of the penicillins should be taken for trivial infections or by patients who have had a previous allergic reaction. About 5 to 15% of the population are liable to be allergic to penicillins or cephalosporins.[83]

Cephalosporins

The cephalosporins, related to the penicillins, are broad spectrum antibiotics. They are loosely categorised into "generations", based on their date of introduction, and their spectrum of activity, particularly against gram-negative bacteria. They are similar to each other in their actions and "there are few absolute indications for their use."[84]

Cephalosporins according to generation

First generation
Injectable: cephalothin, cefazolin, cephaprin
Oral: cephalexin, cefadroxil, cephradine

Second generation
Injectable: cefamandole, cefonicid, cefoxitin, cefotetan, cefuroxime, cefmetazole
Oral: cefaclor, cefuroxime axetil

Third generation
Injectable: moxalactam, cefotaxime, ceftriaxone, ceftizoxime, cefoperazone, ceftazidime
Oral: cefixime

Scrip put the global market for cephalosporins in 1988 at $6.8 billion.[85] The value of the European cephalosporin market was $1.2 billion in 1991, according to a report by Frost & Sullivan.[86] One researcher makes the point that the recent consumption of cephalosporins "has increased so dramatically as to parallel the initial acceptance of penicillin. Organisms that are resistant to the cephalosporins will no doubt continue to thrive."[87]

The American Medical Association (AMA) said in 1980 that "their very active promotion and wide therapeutic usage is out of all proportion to their importance in anti-infective therapy".[88] Six years later, the AMA said that although cephalosporins are generally effective and are used widely, the first and second generation drugs usually "have not been regarded as antibiotics of first choice for the treatment of most infections because of the availability of equally effective and less expensive alternatives". As for the third generation cephalosporins, "additional clinical investigation is required to demonstrate that they are as reliable as the already proven therapeutic agents".[89] One thorough review concluded that "published reports of clinical trials have failed to show superiority of the oral cephalosporins over less expensive alternatives in the treatment of most infections for which they are approved. It is recommended that the oral cephalosporins, especially the newer and more expensive agents, be reserved for second-

attributed in part to heavy marketing. In the first six months of 1988, ciprofloxacin was the second most advertised product in medical journals in the USA.[107]

Promotion of ciprofloxacin has also featured prominently in journals and prescribing guides in developing countries. Not all of the advertisements have been in the best interests of public health. When Bayer launched its brand of ciprofloxacin, Ciprobay, in the Philippines, it ran advertisements which claimed that "Ciprobay is equally effective against gram-positive and gram-negative bacteria alike".[108] However, laboratory tests had shown that ciprofloxacin had weaker activity against gram-positive bacteria. Bayer later admitted that the ads were inaccurate and promised to stop using them. However, the company refused to send letters to physicians explaining the mistake.

Over the years, the advertising has indeed changed. For example, a 1988 two-page advertisement for Ciprobay in Thailand said: "Unknown pathogens, mixed infections, problem organisms... Ciprobay penetrates to the site of infection directly." A headline added the message: "Outstanding broad-spectrum bactericidal activity", while the list of indications read like a who's who of epidemiology: "infections of the respiratory tract, middle ear, sinuses, eyes, kidneys and urinary tract, genital organs (including gonorrhoea), abdomen (e.g. bacterial infections of gastrointestinal tract, biliary tract, peritonitis), skin and soft tissues, bones and joints; further, septicaemia, infections in patients with reduced host defence, selective gut decontamination".[109] By 1991 the advertisements in African journals were simplified even more with the all-embracing headline: "Antibiotic management of bacterial infections", and the list of indications was the same except for the inclusion, in brackets, of the phrase "(due to sensitive organisms)" after the word "infections".[110] The promotion is working: in 1990, global sales of Ciprobay (ciprofloxacin) reached $800 million.[111]

Norfloxacin has proven to be effective in urinary tract infections, including gonococcal infections. However, concentrations of the drug outside the genito-urinary tract are generally far below values necessary to treat systemic infections successfully.[112] Also, quinolones lack effectiveness against *Chlamydia trachomatis*, which frequently accompanies other sexually transmitted disease; therefore, quinolones cannot be used as single-drug therapy for urethritis.[113] The authors of one recent review said: "we do not believe that they are the definitive agents of choice for any specific infection".[114]

An advertisement for Ranbaxy's brand of norfloxacin, Norbactin-400, in India in 1988 included the reassuring – but false – statement: "development of resistance not known".[115] A professor of medicine and pharmacology makes the point that:

> "Properly used, fluoroquinolones have the potential to be effective for many years. Improperly used in the community, nursing home, and hospital, it is possible to rapidly select resistant isolates.... Resistance to one of the new fluoroquinolones causes resistance to all agents of the class, including those still in phase-I study."[116]

By 1989, penicillin-resistant strains of *Neisseria gonorrhoeae* which were also resistant to norfloxacin were found in Canada. The infections were traced to sexual contacts in the Philippines and Thailand. Other reports between 1988 and 1990 also identified quinolone-resistant *N. gonorrhoeae* isolates in the Philippines, the UK and Spain.[117]

At the University Hospital in Uppsala, Sweden, since 1986 all adult bone marrow transplant patients have received oral doses of the quinolone antibiotic, ciprofloxacin, as a prophylaxis against bacterial

Ad for ciprofloxacin (Ciprobay) in TIMS, Thailand, 1988

infection. Since 1987, ciprofloxacin-resistant strains of *S. aureus* have been increasing. By 1989, almost half of such patients were found to have resistant strains, despite protective isolation measures.[118]

Recently, surveys in several countries have confirmed an increasing prevalence of resistance to quinolones among strains of *S. aureus*.[119] During a three-month period in 1989, researchers at a hospital in Pennsylvania, USA found 83 separate bacterial infections resistant to ciprofloxacin. They traced 77 of these to patients from a single nursing home where there was "extensive prescribing" of ciprofloxacin.[120] At a medical centre in Pittsburgh, USA where ciprofloxacin was introduced in January 1988, microbiology reports were showing an increase in resistance during the latter half of 1989. A six-month study which began in November 1989 concluded that prior use of a quinolone antibiotic "was the single most significant risk" for the development of ciprofloxacin resistance.[121]

It is unlikely that any of the quinolones will ever be approved for use in children because animal studies have shown cartilage damage following the administration of these drugs. There have also been reports of reversible bone damage in adolescents who received ciprofloxacin during treatment for cystic fibrosis.[122] The quinolones should also be avoided in pregnancy.[123]

Macrolides and the lincomycin groups

Macrolide antibiotics such as erythromycin are useful in treating tissue infections caused by bacteria resistant to the natural penicillins, or for infections in patients who are allergic to penicillins. However, bacteria quickly become resistant to erythromycin. Heavy clinical use of erythromycin has resulted in the rapid emergence of resistance in certain clinical settings (especially in staphylococci, group A streptococci and enterococci). For example, in one hospital where erythromycin was used as the sole drug to treat penicillin-resistant *S. aureus*, a resistance rate of 70% was found after only five months of clinical use. Resistance to erythromycin has increased significantly among group A streptococci in Japan, Europe and elsewhere.[124]

Erythromycin frequently causes gastrointestinal side effects: nausea, vomiting and diarrhoea. These are dose-related and also commonly occur with the enteric-coated forms of the drug.[125] "There are no adequate data in adults to indicate that any formulation of erythromycin produces fewer gastrointestinal side effects."[126] When Parke-Davis launched its enteric-coated version of erythromycin, Eryc, in Malaysia and Singapore, one of the prominent lines in the advertising was "reduced potential for gastrointestinal upset".[127]

Clindamycin and lincomycin, according to the *British National Formulary* (BNF), "have only a limited use because of their serious side effects."[128] Often, despite clear warnings, misuse still follows.

The AMA says lincomycin "offers no therapeutic advantage over clindamycin. Consequently, it has become obsolete."[129] This "obsolete" drug was marketed by Upjohn in the Philippines in December 1988 for "mild" and "severe" infections.[130] An advertisement for Upjohn's brand of clindamycin, Dalacin C, promoted the drug for "the gram positive infections you see most: tonsillitis, pharyngitis, otitis media, sinusitis, bronchitis, pneumonia, abscesses, skin and soft tissue infections".[131]

Streptomycin and other aminoglycosides

Global sales of aminoglycosides in 1988 reached $620 million.[132] Drugs in this category include gentamicin, amikacin, framycetin, kanamycin, neomycin, netilmicin, paromomycin, sisomicin and tobramycin. They have a broad spectrum of action, but due to resistance and severe side effects their usefulness is limited. They can cause deafness, harm the kidneys and cause muscle weakness and decreased respiration, especially when they are used in high doses or for a long time. They should be given with caution to those past middle age and to patients with kidney problems. They can produce severe allergic reactions. They should not be used in pregnancy.[133] Aminoglycoside-induced hearing loss is a major cause of deafness in China.[134] A multicentre study in the USA found that the average additional cost incurred for each patient who had aminoglycoside-induced kidney damage amounted to $2,500.[135]

The AMA says "data that convincingly show differences in nephrotoxicity [kidney damage] are unavailable," although it adds that some evidence does suggest that tobramycin is probably less nephrotoxic than gentamicin.[136] More recent evidence confirms the probable ranking of gentamicin as most potentially toxic, followed by tobramycin, amikacin, and netilmicin.[137] Recent studies also suggest that the aminoglycosides may well be effective when administered as a single daily dose and that this method of administration can result in lower toxicity.[138]

Streptomycin, according to the BNF, "is now almost entirely reserved for tuberculosis."[139] This is its only indication on the WHO Essential Drugs List.[140] Neomycin is too toxic to be given by injection,[141] or for systemic use.[142] It can be used to sterilise the bowel before surgery. Its main use is in applications for the skin, eyes and ears, but hypersensitivity can occur.

Streptomycin and neomycin are often included in antidiarrhoeal preparations. However, they "should be *avoided* altogether in gastrointestinal infection. They prolong rather than shorten the time taken to control diarrhoea by causing masked bacterial diarrhoea, carrier states or pseudomembranous colitis."[143] Neomycin also causes diarrhoea.[144]

Generally, this entire group of drugs is considered useful in the treatment of *serious* infections which are resistant to penicillin. The two most useful drugs are gentamicin and tobramycin, with amikacin reserved for infections which are resistant to gentamicin and tobramycin.[145]

Chloramphenicol

The "toxic effects" of chloramphenicol, "even though uncommon, have outweighed its usefulness".[146] The BNF states: "Chloramphenicol is a potent, potentially toxic, broad-spectrum antibiotic which should be reserved for the treatment of life-threatening infections."[147] It is valuable for treating typhoid fever and a certain type of meningitis. However, it is widely overprescribed, and its indiscriminate use has led to many unnecessary deaths due to bone marrow damage.[148]

As long ago as 1973, the US Food and Drug Administration (FDA) required chloramphenicol advertisements and package inserts to carry a prominent warning about the drug's possible severe and fatal side effects.[149] However, 10 years later, 49% of all prescriptions for chloramphenicol were still for conditions in which the drug was not indicated, such as for tonsillitis and for the prevention of infection after surgery.[150] Clear warnings have failed to prevent misuse.

In other countries, manufacturers' information is often misleading and inadequate. Overpromotion and lack of adequate information about the dangers of chloramphenicol encourage misuse. In the Philippines in 1988, Farmitalia Carlo Erba was promoting its brand of chloramphenicol, Kemicetine, for "a wide range of therapeutic requirements". Among the indications given for the product were "enteric infections... respiratory infections, infections of the urinary tract".[151]

Chloramphenicol is inexpensive, easy to administer and, if used correctly for a serious condition such as meningitis, the risk of fatal side effects is relatively low in comparison to the risk of death from the disease.[152] Therefore, chloramphenicol should be reserved for use in severe infections, particularly in developing countries. As a leading textbook, *Antibiotics in the Tropics*, says: "chloramphenicol should not be given in trivial infections which can be treated safely with less dangerous agents".[153]

Tetracyclines

Tetracyclines are broad-spectrum antibiotics whose usefulness has decreased as a result of increasing bacterial resistance.[154] They are used much less than previously, at least in industrialised countries. Their uses include the treatment of chronic bronchitis, certain atypical pneumonias and acne. In young children, tetracyclines cause tooth discoloration and increase the risk of tooth decay. They are also deposited in bone and bone growth stops during tetracycline treatments. Therefore, they should *not* be given to children under seven (some say eight or 12) or pregnant women.[155]

In 1986 in Malaysia and Singapore, Lederle was advertising its minocycline product, Minocin, "for the world's fastest growing sexually transmitted disease". The ad claimed that Minocin was "virtually safe. No toxic reactions have been reported to date."[156] However, a 1977 study found that "patients receiving minocycline may experience vestibular toxicity, manifested by dizziness, ataxia, nausea, and vomiting. The symptoms occur soon after the initial dose and generally disappear within 24 to 48 hours after drug administration is stopped. The frequency of this side effect is directly related to the dose and has been noted more often in women than in men."[157] A 1988 advertisement in Thailand described the drug as "the simple treatment of STD", and in particular emphasised its use in treating *Chlamydia trachomatis*.[158] The recommended use of minocycline is now more limited because of the association of the drug with "significant vertigo".[159] Nonetheless, a January 1990 advertisement in *Medecine d'Afrique Noire* in the Central African Republic claimed that Lederle's minocycline was "the treatment of STD of bacterial origin" and that it "prevents sterility".[160]

Minocycline (Minocin) ad, TIMS, Thailand, 1988

Improving antibiotic prescribing

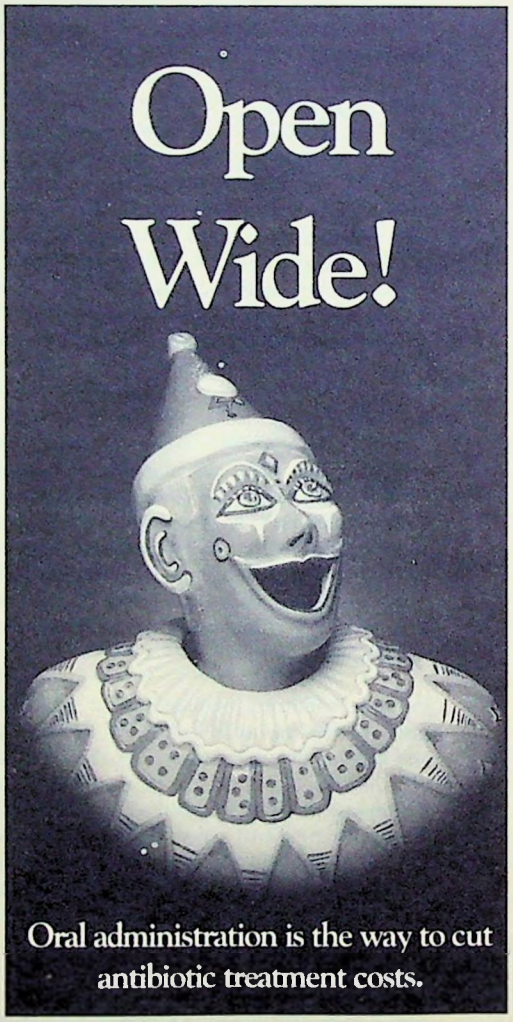
In Australia, a small booklet, *Antibiotic Guidelines*, was published in 1978, and has been regularly updated since, to provide a set of peer-consensus guidelines on antibiotic use. An educational campaign in one hospital to promote the booklet and its advice led to an increase in "appropriate antibiotic treatments" from 52% to 70% from 1978-1982. Two further campaigns in 12 hospitals in 1985 and 1986 led to similar significant improvements in therapy. After costs of the campaigns were taken into account, significant savings were also achieved. The educational campaign made use of an "academic" representative, a mailing of promotional material that promoted rational prescribing, posters throughout the hospitals, lectures, and a humorous video.[1]

At a community health centre in Nebraska, USA, a comprehensive antibiotic sensitivity/prescribing guide that reflects local conditions has been developed to improve antibiotic prescribing. The reaction of physicians has been generally favourable, and the scheme has spread to other hospitals in the area. Doctors have asked for both outpatient and paediatric schemes to also be started.[2]

At a district general hospital in Yorkshire, UK antibiotic prescriptions for surgical prophylaxis changed every six months with each intake of new junior doctors. A survey determined that only 17% of the prescriptions were appropriate. Following the introduction of formal guidelines appropriate prescribing improved to 60% of cases. There were significant cost savings as well.[3]

In Fiji, a training programme for staff from all health centres and nursing stations helped to reduce the inappropriate use of antibiotics in the treatment of acute respiratory infections by almost 50%. Before the training courses started in 1988, antibiotics were incorrectly prescribed for 43% of cough and cold cases. After the training, only 24% of patients with coughs and colds received antibiotics.[4]

The effect of removing an antibiotic restriction policy in operation in a 600-bed hospital in North Carolina, USA holds some lessons for policy makers and administrators. It was felt that the restriction policy was too time consuming and costly to operate. Its removal, however, led to an 158% increase in the number of courses of therapy administered (from 413 during a six-month period of restriction to 1,064 during a six-month period immediately after the lifting of restrictions). Expenditure on antibiotics increased by 103%, from $154,542 to $313,905. There was also an increase in the inappropriate use of at least one of the antibiotics. Researchers studying the change in policy advised others that a plan to remove existing restrictions on antibiotics "should be approached cautiously, as such a step can have a major impact on antimicrobial costs and the quality of care".[5]



Poster used in an Australian campaign to improve antibiotic prescribing.

Sources:
1. Landgren, F.T., Harvey, K.J., et al. "Changing antibiotic prescribing by educational marketing", *Medical Journal of Australia*, Vol 149, 5 19 Dec 1988, pp595-9
2. Snyder, L.L., Clyne, K.E. and Wagner, J.C., "Antibiotic sensitivity and the prescribing information sheet: assisting the prescribing physician", *American Journal of Infection Control*, Vol 18, No 6, Dec 1990, pp399-404
3. Dobrzanski, S., Lawley, D.I., et al. "The impact of guidelines on peri-operative antibiotic administration", *Journal of Clinical Pharmacy and Therapeutics*, Vol 16, 1991, pp19-24
4. Anon., "Towards a more rational use of antibiotics in acute respiratory infections in children", *Essential Drugs Monitor*, No 9, 1990, p5
5. Himmelberg, C.J., Pleasants, R.A., et al. "Use of antimicrobial drugs in adults before and after removal of a restriction policy", *American Journal of Hospital Pharmacy*, Vol 48, Jun 1991, pp1220-7

Co-trimoxazole (trimethoprim and sulfamethoxazole)

Although co-trimoxazole is a useful product, evidence suggests that "trimethoprim by itself can often be used with results equal to that of the combination with regard to efficacy, with perhaps less toxicity".[161]

However, trimethoprim resistance has become a major problem in developing countries.[162] According to WHO, trimethoprim resistance is a particular problem because there is no oral drug that is as effective or as cheap to replace it.[163] It is also a problem in industrialised countries. In many European countries, during the 1970s and 1980s, resistance to trimethoprim among urinary tract bacteria such as *E. coli* increased from less than 10% to 30-40%.[164]

Combinations

Antibiotics given concurrently can be useful in very specific circumstances (for example, as part of a combined treatment in tuberculosis), even though the use of two or more antibiotics at the same time increases the risk of side effects.[165] Fixed-ratio combinations of antibiotics (other than co-trimoxazole) have few indications. There are only two (co-trimoxazole and thiacetazone with isoniazid) on the WHO Essential Drugs List.[166] In the early 1960s, combination antibiotics abounded; however, regulatory authorities such as the US FDA began eliminating them because of insufficient evidence about their efficacy and safety. More recently, some antibiotic products which seem to have a synergistic effect have been introduced after having been reasonably well tested.[167] Principal among these are the combinations of a beta-lactam antibiotic with a drug which inhibits the action of the bacterial enzymes (beta-lactamases) which render the antibiotic ineffective. Two such beta-lactamase inhibitors, clavulanic acid and sulbactam, are now commonly found in fixed-ratio combinations with amoxycillin, ticarcillin or ampicillin. However, even the new combination products are not without their problems of resistance.[168]

In many countries, inappropriate antibiotic combinations abound. According to Dr Edmundo Ferraz, president of the Brazilian Association for the Control of Hospital Infections, 390 of the 795 antibiotics on the market in Brazil should be withdrawn because they are "inappropriate" combinations which can "cause severe damage to health". In evidence submitted to the Brazilian Health Minister, he says that resistance to antibacterials in Brazil has become a real problem due to the inappropriate use of these drugs.[169]

Policies for the future

It is commonly believed that the only way to combat growing resistance to antibiotics is to produce new, more effective drugs. This race for a "wonder drug" to beat the "super bug" is misleading. The real solution is to eliminate misuse. As one study concluded, "rather than attempt to overcome or pre-empt resistance by prescribing yet another agent, the objective should be to prevent resistance by limiting the amount of antibiotic prescriptions".[170]

Certainly, having more new drugs won't change the way they are being used. In fact, as one commentator has pointed out:

> "New agents should be reserved for specific indications – eg, infections caused by organisms resistant to standard drugs, or infections in which the newcomer has been proven superior to earlier agents by comparative clinical trial."[171]

A WHO expert committee has suggested that in addition to the Essential Drugs List which included 16 antibiotics, a "reserve list" of antibiotics should be set up which could include some of the third-generation cephalosporins, quinolones and vancomycin. Such antibiotics, although effective in a wide range of infections, are inappropriate for unrestricted use either because of the need to reduce the risk of resistance to them, or because of their high cost.[172]

The question of cost is certainly worth considering. In no area of medicine are differences in cost more apparent than in the selection of antibiotics. For example, amoxycillin, co-amoxiclav, co-trimoxazole, erythromycin, cefaclor and tetracycline are common antibiotic choices for outpatient treatment of community-acquired upper respiratory infections. None of these antibiotics is clearly superior for initial treatment; however, co-amoxiclav and cefaclor cost at least three times more than the others (in the USA) and clearly should be reserved for special situations or resistant organisms.[173] A study in Canada found that, as a general rule, most new drugs are two to four times more expensive than antibiotics that have been on the market for several years.[174]

Without control, there are severe dangers ahead. In response to this, in September 1984, a large conference was organised by the US National Institutes of Health (NIH) and WHO to look into the problem more closely than ever before. This conference posed a threat to the pharmaceutical industry. It was

> "... effectively thwarted by the pharmaceutical industry and resulted in a little more 'than a pathetic call for further studies'.... We should all keep a closer eye upon the pharmaceutical companies. If a company is marketing obsolete antimicrobials in developing countries or conducting policies which will promote resistance to the newest agents the prescribers and regulatory agencies in other countries should simply ask: Why? Marketing antimicrobials is not only a matter of money; it is a matter of ethics as well.... We have to tell our friends in the pharmaceutical companies that we do

indeed need some of their products, but we certainly do not always agree with their policy. One may expect the wiser companies to take a hint as to how to behave; where a company does not, its products should be removed from the market. The question of the worldwide increase in resistance is too serious to be hampered by concerns about freedom and profits."[175]

The industry, having helped to turn a life-saving group of products into a group of potentially life-threatening ones, is now trying to obstruct major efforts to rescue the situation. The resistance of the drug industry to change is as dangerous as the resistance of bacteria to antibiotics.

A recent review in the *New England Journal of Medicine* points out that:

"If current practice prevails, the trends in antimicrobial resistance seen in the past decade will continue into the next century. Developing countries and hospitals will be the breeding grounds and reservoirs for the evolution and maintenance of resistance genes and multi-resistant strains that will impede both current and future chemotherapy. There are two chief areas of concern. The first is that pathogens for the normal host will acquire a critical complement of resistance and virulence genes, leading to widespread dissemination and serious infections in the community. The second is that bacteria resistant to all available chemotherapy will become the predominant nosocomial [hospital-acquired] pathogens."[176]

Several leading experts in the field of infection control constantly reinforce the need for responsible, rational use of antibiotics.

"The pharmaceutical chemists still remain one jump ahead of the bacteria. How long this can continue depends not only upon the ingenuity of the chemists but far more importantly upon a conservative approach to antimicrobial chemotherapy by clinicians."[177]

"We have never been much more than one step ahead, and now it seems that this slender lead is in danger of being lost. We must therefore strain every sinew to use antibiotics in a responsible fashion."[178]

"Decreased use of antibiotics will ultimately reduce the pool of resistance genes and... improved hygiene will decrease the need for antibiotics and the transmission of bacteria through close contact. Those who prescribe and use antibiotics need to develop a greater respect for their long-range ecological effects."[179]

"Use antibiotics appropriately: this means using as narrow a spectrum antibiotic as possible, restricting the dose and duration of treatment to the minimum that is optimal, being especially careful when prescribing prophylactic antibiotics, and formulating and adhering to an agreed Antibiotic Policy."[180]

[See also the sections on *Antidiarrhoeals*, *Antidiarrhoeals containing antibiotics*, *Cough and cold preparations*, and *Drugs in pregnancy*.]

Recommendations for action

1. Antibiotics with a potential for serious risk, such as *chloramphenicol* or systemic *neomycin*, yet with one or two useful indications, should be placed under severe restriction. Wherever possible, they should be withdrawn from the general market and be prescribed by specialists who are familiar with their potential risks.
2. Antibiotic combinations (except those such as co-trimoxazole or those with chemicals such as clavulanate or sulbactum) should be banned.
3. Governments in all countries should develop strict antibiotic policies as part of a national drug policy. These should include:
   a) a limited list of antibiotics, with some kept in reserve for use against micro-organisms resistant to first-line drugs;
   b) a regularly revised set of therapeutic guidelines;
   c) drug utilisation studies to monitor the use of antibiotics and, where necessary, the introduction of education programmes to encourage the rational use of antibiotics.
4. Product information should carry a clear warning about the problems of resistance and the need for careful diagnosis and selective use.
5. Governments may wish to consider introducing bans, or other controls, on the advertising of antibiotics, as the information contained in manufacturers' promotional materials has been implicated in poor prescribing habits.
6. Health authorities should introduce regular refresher courses and other independent exchanges of information on antibiotics for health workers. One of the most important messages to communicate is that new antibiotics should be used cautiously and often kept in reserve for the treatment of serious infections that prove to be resistant to other antibiotics.

References:

1. Anon., "Who is responsible for these unnecessary typhoid deaths?", *ACASH News*, Dec 1990, p1
2. Australian microbiologist Dr Ken Harvey, quoted in: de Bruxelles, S. and Ferriman, A., "Deadly 'super bug' spreads through wards", *Observer* (London), 31 Aug 1986
3. Murray, B.E., "New aspects of antimicrobial resistance and the resulting therapeutic dilemmas", *Journal of Infectious Diseases*, Vol 163, Jun 1991, pp1185-94
4. Geddes, A.M., "Antibiotic therapy – a resumé", *Lancet*, 6 Feb 1988, pp286-9
5. Neu, H.C., "Antimicrobial agents: the old and the new", *American Journal of Infection Control*, Vol 17, No 5, Oct 1989, pp276-85
6. O'Brien, T.F., et al, "Resistance of bacteria to antibacterial agents: report of Task Force 2", *Reviews of Infectious Diseases*, Vol 9 (Suppl. 3), May-Jun 1987, ppS244-60
7. Lester, S.C., Pla, M.dP, et al, "The carriage of *Escherichia coli* resistant to antimicrobial agents by healthy children in Boston, in Caracas, Venezuela, and in Qin Pu, China", *New England Journal of Medicine*, Vol 323, No 5, 2 Aug 1990, p285-9
8. de Groot, R., *Antibiotic Resistance in Haemophilus influenzae*, Rotterdam, Erasmus University, 1991, p13
9. Jacoby, G.A. and Archer, G.L., "New mechanisms of bacterial resistance to antimicrobial agents", *New England Journal of Medicine*, Vol 324, No 9, 28 Feb 1991, pp601-12; Halliday, J., *Antibiotics: The Comprehensive Guide*, London, Bloomsbury, 1990, pxviii; de Groot, op cit, pp24-7
10. Jacoby and Archer, op cit, pp601-12; Halliday, op cit, pxviii; Henry, J. (ed.), *The British Medical Association Guide to Medicines & Drugs*, London, Dorling Kindersley, (2nd edn) 1991, p124
11. Levy, S.B., "Starting life resistance-free", *New England Journal of Medicine*, Vol 323, No 5, 2 Aug 1990, pp335-7
12. O'Sullivan, N. and Wise, R., "Macrolide, lincosamide, and streptogramin antibiotics", *Current Opinion in Infectious Diseases*, Vol 3, 1990, pp743-50; de Groot, R., op cit, p20
13. Reed, B.D., Huck, W., and Zazove, P., "Treatment of beta-hemolytic streptococcal pharyngitis with cefaclor or penicillin: efficacy and interaction with beta-lactamase-producing organisms in the pharynx", *Journal of Family Practice*, Vol 32, No 2, 1991, pp138-44
14. Hamilton-Miller, J.M.T., "The emergence of antibiotic resistance: myths and facts in clinical practice", *Intensive Care Medicine*, Vol 16 (Suppl. 3), 1990, ppS206-11
15. Anon., 'WHO/ATH on the misuse of antibiotics', *Scrip*, No 1272/3, 8/13 Jan 1988, p26; O'Neill, P. and McIntosh, S., 'Bacteria resistant to antibiotics spread concern', *New Scientist*, 27 Aug 1987, p16
16. Marton, A., Gulyas, M., et al, "Extremely High Incidence of Antibiotic Resistance in Clinical Isolates of *Streptococcus pneumoniae* in Hungary", *Journal of Infectious Diseases*, 163, 3, Mar 1991, 542-8
17. Fenoll, A., Bourgon, C.M., et al, "Serotype distribution and antimicrobial resistance of *Streptococcus pneumoniae* isolates causing systemic infections in Spain, 1979-1989", *Reviews of Infectious Diseases*, Vol 13, No 1, Jan-Feb 1991, 56-60
18. Anon., 'WHO on multiresistant bacteria', *Scrip*, No 1290, 11 Mar 1988, p20
19. Barnes, R.C., Holmes, K.K., "Epidemiology of gonorrhea: current perspectives", *Epidemiology Review*, Vol 6, 1984, pp1-30
20. Czachor, J.S. and Gleckman, R.A., "Third-generation cephalosporins: a plea to save them for specific infections", *Postgraduate Medicine*, Vol 85, No 4, Mar 1989, pp169-176; van Klingeren, B., Dessens-Kroon, M., Verheuvel, M., "Increased tetracycline resistance in gonococci in The Netherlands", *Lancet*, 25 Nov 1989, p1278
21. Salam, M.A. and Bennish, M.L., "Antimicrobial therapy for shigellosis", *Reviews of Infectious Diseases*, Vol 13, Suppl. 4, Mar-Apr 1991, pS336
22. de Groot, op cit, pp46-7
23. Pecoul, B., Varaine, F., et al, "Long-acting chloramphenicol versus intravenous ampicillin for treatment of bacterial meningitis", *Lancet*, Vol 338, No 8771, 5 Oct 1991, pp862-6
24. Brumfitt, W. and Hamilton-Miller, J., "Methicillin-resistant *Staphylococcus aureus*", *New England Journal of Medicine*, Vol 320, No 18, 4 May 1989, pp1188-96
25. Maple, P.A.C., Hamilton-Miller, J.M.T. and Brumfitt, W., "World-wide antibiotic resistance in methicillin-resistant *Staphylococcus aureus*", *Lancet*, 11 Mar 1989, pp537-40
26. Levy, op cit, pp335-7
27. Jacoby and Archer, op cit, pp601-12
28. de Groot, op cit, p19
29. Anon., 'Antibiotic usage in Uruguay', *Scrip*, No 1276, 22 Jan 1988, p24; Anon., 'Importance of training in EDP', *Scrip*, No 1355, 26 Oct 1988, p20; Anon., 'Kuwait's antibiotic consumption', *Scrip*, No 1335, 17 Aug 1988, p21; Anon., 'Misuse of antibiotics in Pakistan', *Scrip*, No 1339, 31 Aug 1988, p21; Anon., 'Inappropriate use of antibiotics in New Zealand', *Scrip*, No 1313, 1 Jun 1988, p20; Anon., 'Combination antibiotics questioned in Brazil', *Scrip*, No 1296, 1 Apr 1988, p18; Anon., *Scrip*, No 1272/3, 8/13 Jan 1988, op cit, p26; Anon., *Scrip*, No 1290, 11 Mar 1988, op cit, p20
30. Anon., "Swedish antibiotic use in 1988", *Scrip*, No 1479, 12 Jan 1990, p8
31. Henry, op cit, p124
32. Harvey, K., 'Antibiotic use in Australia', *Australian Prescriber*, Vol II No 4, 1988, pp74-7
33. Jackson, D.M. and Soothill, R., *Is the Medicine Making You Ill?*, North Ryde, Australia, Angus & Robertson, 1989, p12
34. Chilnick, L.D. (ed.), *The Pill Book*, New York, Bantam Books, (4th edn) 1990, p946
35. Levy, op cit, pp335-7
36. Kunin, C.M., "The responsibility of the infectious disease community for the optimal use of antimicrobial agents", *Journal of Infectious Diseases*, Vol 151, No 3, Mar 1985, pp388-98
37. Black, G.J. (ed.), *Physician's 1990 Drug Handbook*, Springhouse, PA, Springhouse Corporation, 1990, px
38. Wolfe, S.M., Fugate, L., et al, *Worst Pills Best Pills*, Washington, Public Citizen Health Research Group, 1988, p343
39. Parish, P., *Medicines: a guide for everybody*, London, Penguin (6th edn, revised), 1989, p284
40. Frieden, T.R. and Mangi, R.J., "Inappropriate use of oral ciprofloxacin", *Journal of the American Medical Association*, Vol 264, No 11, 19 Sep 1990, pp1438-40
41. O'Neill and McIntosh, op cit, p16
42. Hamilton-Miller, op cit, ppS206-11
43. Lexchin, J., "Doctors and detailers: therapeutic education or pharmaceutical promotion?", *International Journal of Health Services*, Vol 19, No 4, 1989, p675
44. Anon., "'Indiscriminate' antibiotic use in Italy", *Scrip*, No 1616, 15 May 1991, p8
45. Harvey, 1988, op cit, pp74-7
46. Anon., *Scrip*, No 1313, 1 Jun 1988, op cit, p20
47. Jones, R.N., "Role of new cephamycins in the management of obstetric and gynecologic infections", *Journal of Reproductive Medicine*, Vol 35, No 11, (suppl.) Nov 1990, pp1070-7
48. WHO, *The Use of Essential Drugs*, (Technical Report Series No 770), Geneva, WHO, 1988, pp33-4. (The figure excludes drugs for parasitic infections, for leprosy and for tuberculosis.)
49. Parish, op cit, p283
50. Schlegel, P.N., Chang, T.S.K. and Marshall, F.F., "Antibiotics: potential hazards to male fertility", *Fertility and Sterility*, Vol 55, No 2, Feb 1991, pp235-42
51. Steele, R.W. and Kearns, G.L., "Antimicrobial therapy for pediatric patients", *Pediatric Clinics of North America*, Vol 36, No 5, Oct 1989, pp1321-49
52. Schorling, J.B., de Souza, M.A. and Guerrant, R.L., "Patterns of antibiotic use among children in an urban Brazilian slum", *International Journal of Epidemiology*, Vol 19, No 4, 1991, pp293-9
53. Salam and Bennish, op cit, pS335
54. WHO, *The treatment and prevention of acute diarrhoea: Practical guidelines*, Geneva, WHO, (2nd edn) 1989, p3
55. Anon., *Scrip*, No 1276, 22 Jan 1988, op cit, p24
56. Obaseiki-Ebor, E.E., Akerele, J.O. and Ebea, P.O., "A survey of antibiotic outpatient prescribing and antibiotic self-medication", *Journal of Antimicrobial Chemotherapy*, 1987, pp759-63
57. Anon., *Scrip*, No 1355, 26 Oct 1988, op cit, p20
58. Anon., *Scrip*, No 1335, 17 Aug 1988, op cit, p21
59. Antibiotic Guidelines Sub-Committee, Health Dept of Victoria; *Antibiotic Guidelines* (5th edn), Toorak, Victorian Medical Postgraduate Foundation, 1987, p11
60. Enenkel, S. and Stille, W., *Antibiotics in the Tropics: antibacterial therapy with limited resources*, Berlin, Springer-Verlag, 1988, p34
61. Obaseiki-Ebor, et al, op cit, pp759-63
62. Misago, C. and Fonseca, W., "Antimicrobial drugs advised in pharmacies in Brazil for children with acute respiratory infections", *Lancet*, Vol 338, No 8768, 14 Sep 1991, p702
63. Pratt, W.B. and Fekety, R., *The Antimicrobial Drugs*, Oxford, Oxford University Press, 1986, p14
64. Erlichman, J., *Gluttons for Punishment*, London, Penguin, 1986, p44
65. Spika, J.S., Blake, P.A. and Cohen, M.L., "Chloramphenicol-resistant *Salmonella newport* traced through hamburger to dairy farms", *New England Journal of Medicine*, 3 Sep 1987, p632; Ryan, C.P. and Steele, J.H., "Chloramphenicol-resistant *Salmonella newport* traced through hamburger to dairy farms", *New England Journal of Medicine*, 3 Sep 1987, p632
66. de Groot, op cit, pp20-1
67. Erlichman, op cit, pp58 and 47
68. Okolo, M.I. "Bacterial drug resistance in meat animals: a review", *Int J Zoonoses*, Vol 13, No 3, Sep 1986, pp143-52
69. Piddock, L.J.V., Wray, C., et al; "Quinolone resistance in *Salmonella* spp: veterinary pointers", *Lancet*, 14 Jul 1990, p125
70. Anon., "8% growth for anti-infective market", *Scrip*, No 1791, 2 Feb 1993, p25
71. *Scrip's 1991 Antibacterial Report*, London, PJB Publications, 1991 (One source estimates that the market will be worth more than $25 billion by 1995; see: Anon., "Searle launches Maxaquin in Mexico", *Scrip*, No 1598, 13 Mar 1991, p22.)
72. Geddes, op cit, pp286-9; Liss, R.H. and Batchelor, F.R., "Economic evaluations of antibiotic use and resistance – a perspective: report of Task Force 6", *Reviews of Infectious Diseases*, Vol 9 (Suppl. 3), May-Jun 1987, ppS297-312
73. Frieden and Mangi, op cit, pp1438-40; also reported in: Anon., "Overuse of ciprofloxacin in US?", *Scrip*, No 1558, 17 Oct 1990, p26
74. Hemminki, E., "Adverse reactions to antibiotic drugs: the present scope of the problem in outpatient care and possibilities for improvement", *International Journal of Health Services*, Vol 11, No 2, 1981, pp283-301
75. Wyatt, T.D., Passmore, C.M., et al, "Antibiotic prescribing: the need for a policy in general practice", *British Medical Journal*, Vol 300, 17 Feb 1990, pp441-4
76. Carlson, J.A., "Antimicrobial formulary management: meeting the challenge in a health maintenance organization", *Pharmacotherapy*, Vol 11, No 1 (suppl.), 1991, pp32S-35S
77. Lappé, M., *When Antibiotics Fail*, Berkeley, Calif., North Atlantic Books, 1986, p96
78. Anon., 'Drug promotional problems', *Medical Journal of Australia*, Vol 150, 17 Apr 1989, p463
79. *Scrip's 1990 Antibacterial Report*, London, PJB Publications, 1990

80. Anon., "Top 20 branded products of 1988", *Scrip*, No 1481, 19 Jan 1990, p24 (based on estimates reported in Flemings Research's *Pharmaceutical Products Worldwide*); Anon., "Ten 'key' drugs to boost SB", *Scrip*, No 1614/15, 8 & 10 May 1991, p10
81. Parish, op cit, p286
82. IFPMA, *IFPMA Code of Pharmaceutical Marketing Practices*, Geneva, IFPMA, 1989, p6
83. Liu, H.H., "Antibiotics and infectious diseases", *Primary Care*, Vol 17, No 4, Dec 1990, pp745-74
84. BMA and the Royal Pharmaceutical Society of Great Britain, *British National Formulary*, London, BMA and The Pharmaceutical Press, No 22, Sep 1991, p196
85. *Scrip's 1990 Antibacterial Report*, op cit
86. Anon., "European antibiotic mkt projections", *Scrip*, No 1591, 15 Feb 1991, p6 (citing a 1991 Frost & Sullivan report, *The European market for antibiotic products*)
87. Gentry, L.O., "Newer concepts in antimicrobial therapy", *Clinical Orthopaedics and Related Research*, No 261, Dec 1990, pp23-6
88. AMA, *Drug Evaluations*, Philadelphia, W.B. Saunders Co., (4th edn) 1980, p1230
89. AMA, *Drug Evaluations*, Philadelphia, W.B Saunders Co., (6th edn) 1986, p1344
90. Smith, G.H., "Oral cephalosporins in perspective", *DICP, The Annals of Pharmacotherapy*, Vol 24, Jan 1990, pp45-51
91. Czachor and Gleckman, op cit, pp169-176
92. Antibiotic Guidelines Sub-Committee, op cit, p15
93. Karam, G.H., Saunders, C.V., and Aldridge, K.E., "Role of newer antimicrobial agents in the treatment of mixed aerobic and anaerobic infections", *Surgery, Gynecology & Obstetrics*, (suppl. to vol 172) 1991, pp57-64
94. Chapman, S.T. and Walsh, T.H., "Which Antibiotic for Surgical Nosocomial Infection?" *British Journal of Clinical Practice*, Vol 45, No 2, Summer 1991, pp141-4
95. Rodriguez, W.J. and Wiedermann, B.L., "Progress in antibacterial therapy: cephalosporins and quinolones", *Advances in Pediatric Infectious Diseases*, Vol 4, 1989, pp183-210
96. AMA, 1986, op cit, p1369
97. Advertisement in *Thailand Index of Medical Specialities*, Vol 17, No 3, Nov 1988, facing p212
98. Anon., "Hoechst pharma analysed", *Scrip*, 25 Nov 1985, p7
99. Anon., "Hoechst's 1990 pharma sales up 2%", *Scrip*, No 1619, 24 May 1991, p10
100. Advertisement in Quereshi, A.H. (ed.), *Quick Index of Medical Preparations*, Nos 1 & 2, Mar-Aug 1990, facing p2A
101. Ibid, facing p93
102. Neu, op cit, pp276-85
103. DiNubile, M.J., "Antibiotics: the antipyretics of choice?", *American Journal of Medicine*, Vol 89, Dec 1990, pp787-8
104. Liu, op cit, pp745-74
105. Anon., *Scrip*, No 1598, 13 Mar 1991, op cit, p22
106. Anon., *Scrip*, No 1591, 15 Feb 1991, op cit, p6
107. Frieden and Mangi, op cit, pp1438-40; reported in: Anon., *Scrip*, No 1558, 17 Oct 1990, op cit, p26; and in: Anon., "Quinolones: costs and benefits", *Drug Monitor* (Philippines), Vol VI, No 4, Apr 1991, p42
108. Tan, M.L., *Dying for Drugs: Pill power and politics in the Philippines*, Manila, Health Action Information Network, 1988, pp142-3
109. Advertisement in *Thailand Index of Medical Specialities*, op cit, facing p234
110. Advertisement in *MIMS Africa*, Vol 31, No 4, Jul 1991, p73
111. Anon., "Top 50 branded products worldwide", *Scrip*, Review issue 1990, p21 (based on Barclay de Zoete Wedd's Pharmaceutical Industry Perspectives)
112. Steele and Kearns, pp1321-49
113. Rodriguez and Wiedermann, op cit, pp183-210
114. Hooper, D.C. and Wolfson, J.S., "Fluoroquinolone antimicrobial agents", *New England Journal of Medicine*, Vol 324, No 6, 7 Feb 1991, pp384-94
115. Advertisement in *MIMS India*, Vol 8, No 2, Feb 1988, p83
116. Neu, op cit, pp276-85
117. Yeung, K.H. and Dillon, J.R., "Norfloxacin resistant *Neisseria gonorrhoeae* in North America", *Lancet*, Vol 336, No 8717, 22 Sep 1990, p759; Jephcott, A.E. and Turner, A., "Ciprofloxacin resistance in gonococci", *Lancet*, Vol 335, No 8682, 20 Jan 1990, p165
118. Hedin, G and Hambraeus, A., "Multiply antibiotic-resistant *Staphylococcus epidermidis* in patients, staff and environment – a one-week survey in a bone marrow transplant unit", *Journal of Hospital Infection*, Vol 17, 1991, pp95-106
119. Trucksis, M., Hooper, D.C. and Wolfson, J.S., "Emerging resistance to fluoroquinolones in staphylococci: an alert", *Annals of Internal Medicine*, Vol 114, No 5, 1 Mar 1991, pp424-6
120. Anon., "Emerging ciprofloxacin resistance", *Scrip*, No 1566, 14 Nov 1990, p28
121. Muder, R.R., Brennen, C., et al, "Association with prior fluoroquinolone therapy of widespread ciprofloxacin resistance among gram-negative isolates in a Veterans Affairs medical center", *Antimicrobial Agents and Chemotherapy*, Vol 35, No 2, Feb 1991, pp256-8
122. Steele and Kearns, op cit, pp1321-49
123. Liu, op cit, pp745-74
124. Moellering, R.C., "Introduction: Revolutionary changes in the macrolide and azalide antibiotics", *American Journal of Medicine*, Vol 91 (Suppl. 3A), 12 Sep 1991, p3A-2S
125. Rodnick, J.E. and Gude, J.K., "Diagnosis and antibiotic treatment of community-acquired pneumonia", *Western Journal of Medicine*, Vol 154, Apr 1991, pp405-9
126. Hampson, N.B., Woolf, R.A. and Springmeyer, S.C., "Oral antibiotics for pneumonia", *Clinics in Chest Medicine*, Vol 12, No 2, Jun 1991, pp395-407
127. Advertisement in *Drug Index for Malaysia & Singapore*, Vol 15, No 2, Jun 1986, facing p16
128. BMA and the Royal Pharmaceutical Society of Great Britain, op cit, p205
129. AMA, 1986, op cit, p1405
130. Advertisement and product listing in *Philippine Index of Medical Specialities*, Vol 17, No 3, Dec 1988, pp217-18
131. Ibid, p216
132. *Scrip's 1990 Antibacterial Report*, op cit
133. Parish, op cit, pp290-1
134. Hu, D.-N., Qiu, W.Q., et al, "Genetic aspects of antibiotic induced deafness: mitochondrial inheritance", *Journal of Medical Genetics*, Vol 28, 1991, pp79-83
135. Wilson, S.E., "Aminoglycosides: assessing the potential for nephrotoxicity", *Surgery, Gynecology & Obstetrics*, Vol 171 (Suppl.), 1990, pp24-30
136. AMA, 1986, op cit, p1434
137. Steele and Kearns, op cit, pp1321-49
138. Neu, op cit, pp276-85; Bergogne-Berezin, E., "Current trends and new perspectives in antibiotic therapy", *Journal of Chemotherapy*, Vol 1, No 5, 1989, pp285-92
139. BMA and the Royal Pharmaceutical Society of Great Britain, op cit, p202
140. WHO, 1988, op cit, p35
141. BMA and the Royal Pharmaceutical Society of Great Britain, op cit, p203
142. Parish, op cit, p291
143. BMA and the Royal Pharmaceutical Society of Great Britain, op cit, p36
144. AMA, 1986, op cit, p1446
145. Reynolds, J.E.F. (ed.), *Martindale: The Extra Pharmacopoeia*, London, The Pharmaceutical Press, (29th edn) 1989; BMA and the Royal Pharmaceutical Society of Great Britain, op cit; AMA, 1986, op cit
146. Cawson, R. and Spector, R., *Drugs and Medicines: a consumers' guide*, Oxford, Oxford University Press, 1990, p37
147. BMA and the Royal Pharmaceutical Society of Great Britain, op cit, p206
148. Parish, op cit, p292
149. Dunne, M., et al, "Indications and warnings about chloramphenicol", *Lancet*, 6 Oct 1973, pp781-3
150. Wolfe, et al, op cit, p343
151. Advertisement and product listing in *Philippine Index of Medical Specialities*, Vol 17, No 3, Dec 1988, p175
152. Pecoul, et al, op cit, pp862-6
153. Enenkel and Stille, op cit, p14
154. BMA and the Royal Pharmaceutical Society of Great Britain, op cit, p200
155. Parish, op cit, p290
156. Advertisement in *Drug Index for Malaysia and Singapore*, Vol 15, No 2, Jun 1986, facing p189
157. A.G., Rall, T.W., Nies, A.S., and Taylor, P., *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, New York, Pergamon Press, (8th edn) 1990, p1122 (quoting a 1977 study by Fanning, W.L., et al, "Side effects of minocycline: a double-blind study", *Antimicrobial Agents and Chemotherapy*, Vol 11, 1977, pp712-17)
158. Advertisement in *Thailand Index of Medical Specialities*, Vol 17, No 3, Nov 1988, facing p230
159. Liu, op cit, pp745-74
160. Letter from MaLAM to Lederle Laboratories, Feb 1991
161. Hollister, L.E. (ed.), *1988 Year Book of Drug Therapy*, Chicago, Year Book Medical Publishers, 1988, p191
162. de Groot, op cit, pp35-7, 53-4
163. WHO, *The World Drug Situation*, Geneva, WHO, 1988, p19
164. de Groot, op cit, pp35-6
165. Pauly, D.J., Musa, D.M., et al, "Risk of nephrotoxicity with combination vancomycin-aminoglycoside antibiotic therapy", *Pharmacotherapy*, Vol 10, No 6, 1990, pp378-82
166. WHO, 1988, op cit
167. Steele and Kearns, op cit, pp1321-49
168. French, G. and Ling, T., "Amoxycillin/clavulanic acid resistant *Escherichia coli*", *Lancet*, 26 Mar 1988, p704
169. Anon., *Scrip*, No 1296, 1 Apr 1988, op cit, p18
170. Wyatt, et al, op cit, pp441-4
171. Geddes, op cit, pp286-9
172. Anon., "WHO proposes 'reserve antibiotics'", *Scrip*, No 1493, 2 Mar 1990, p28
173. Friedman, R.B. and Katt, J.A., "Cost-benefit issues in the practice of internal medicine", *Archives of Internal Medicine*, Vol 151, Jun 1991, pp1165-8
174. Bergeron, M.G., "The future of new oral antibiotics including the quinolones", *Canadian Medical Association Journal*, Vol 138, 1 Jan 1988, pp35-42
175. Midtvedt, T., "Increasing worldwide microbial resistance: a worldwide responsibility for all, including the pharmaceutical industry and the World Health Organisation", in Dukes, M.N.G. and Beeley, L. (eds), *Side Effects of Drugs Annual 12*, Amsterdam, Elsevier, 1988, pp206-8
176. Jacoby and Archer, op cit, pp601-12
177. Wise, R., "Antimicrobial agents: a widening choice", *Lancet*, 28 Nov 1987, pp1251-4
178. Hamilton-Miller, op cit, ppS206-11
179. Levy, op cit, pp335-7
180. Hamilton-Miller, op cit, ppS206-11

Chetley, A. *Problem Drugs*, Amsterdam,
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4A. Analgesics

Killing pain

True or false?: "You can't buy a more potent pain reliever without a prescription" – Extra Strength Tylenol. "Tylenol provides relief without the stomach irritation you can get from aspirin or Advil". Anacin-3 "recommended over five million times for headaches and other kinds of pain". Bufferin "reaches the bloodstream twice as fast". According to Manhattan US District Court Judge William C. Conner, all the claims are untrue or misleading. After a two-year suit and countersuit between Johnson & Johnson and American Home Products who were contesting for supremacy in the $1.8 billion over-the-counter (OTC) pain killer market in the USA, his 65-page decision included the comment: "Small nations have fought for their very survival with less resources and resourcefulness than these antagonists have brought to their epic struggle for commercial primacy in the OTC analgesic field."[1]

Pain is one of the most common of symptoms, and one of the most frequent reasons why people seek medical care.[2] It is not surprising, therefore, that analgesics (pain killers) are among the most used categories of drugs.[3] In 1981, about 9% of all drug prescriptions in the USA were for analgesics and associated medications.[4] In the UK in 1989, sales of analgesics accounted for 20% of the total market for OTC drugs.[5] The US market for pain management products – which includes prescription drugs, OTC drugs, devices and alternative therapies – stood at US $5 billion in 1988 and is expected to exceed $7.8 billion by 1995, of which an estimated $4.04 billion will be for prescription drugs, and $3.61 billion will be spent on OTC products.[6] By 1995 the European market for all types of pain relief products is expected to reach $7 billion.[7]

The human body has thousands of nerve endings, highly sensitive to pain, scattered throughout various tissues. When tissue is damaged due to injury or infection, chemicals called prostaglandins are produced. These prostaglandins act on the nerve endings so that a message is sent along the nerves to the brain and we respond with the feeling of pain – "an unpleasant sensory and emotional experience".[8]

Pain is not simply a *perception*. It is a complex phenomenon or syndrome, only one component of which is the sensation actually reported as pain. Pain has four major components: nociception (the impact of the local injury or trauma on the nerve endings or nociceptors); the perception of pain which is a psychological state; suffering as a consequence of the pain (which usually manifests as anxiety in the case of acute pain and depression in the case of chronic pain); and pain behaviour (facial expression, restlessness, seeking isolation or company, medicine taking, and so on).[9] It is at least partially a learned response.[10]

Animal studies have shown that pain and stress can inhibit immune function and enhance tumour growth. One of the leading experts on pain, Dr Ronald Melzack, expressed it plainly when he told colleagues at the Fifth World Congress on Pain, "Pain can... have a major impact on morbidity and mortality... it can mean the difference between life and death."[11]

Pain is usually described as *acute* or *chronic*, with the difference being based on the time a pain lasts. For example, chronic pain is usually defined as pain which persists past the expected normal time of healing,[12] while acute pain can be defined as an event whose end can be predicted.[13] At least among children, it has been suggested that there should be three categories: acute pain, cancer pain, and chronic non-malignant pain.[14] Most paediatric pain is acute and self-limiting. The recurrent pains of childhood – headaches, abdominal cramping, and limb pains – seldom need pharmacological therapy unless an organic basis exists.[15]

Chronic pain is one of the costliest of today's health problems in industrialised countries. It has been estimated to affect 25-30% of the populations in industrialised countries.[16] In the USA, the overall cost of pain amounts to nearly $90 billion a year.[17]

Treating pain

Although acute pain can often be dealt with in a relatively simple manner, dealing with chronic pain is a much more complex matter, one which more and more is coming to rely on a multidisciplinary approach that takes into account a wide range of therapies and support mechanisms.[18]

The best way to treat acute pain is to attempt to remove the underlying cause. A pain killer should be used only when the cause of the pain cannot be removed.[19] One of the reasons for this is that analgesics do not take the cause of the pain away, they simply reduce the response produced by the pain. However, the relief of pain does not necessarily depend on the use of analgesics. Cold water applied to a skin burn may relieve the pain; heat or massage may relieve muscle pain; an alkali mixture may relieve the pain of a peptic ulcer. Recently too, evidence has been emerging from clinical studies to suggest that acupuncture or electrical nerve stimulation across the skin (transcutaneous) can relieve some types of pain.[20] It is also worth remembering the 1955 study by Henry K. Beecher which found that 35% of people suffering from a variety of painful conditions experienced relief when they were given a placebo.[21]

However, much misprescribing of pain killers seems to occur. One study of 500 patients with headache in Italy found that the treatments prescribed by doctors "varied widely, seemed not to be closely correlated with the subtype of headache (e.g. migraine, muscle contraction), and seemed not to reflect the recommendations given in controlled studies in the scientific literature. A very large number of drugs were used [76 different drugs], often in combinations, and some had scant or no rationale for use for the indication of headache."[22]

One doctor points out that most of the analgesics on the market are simply "alternatives of fashion or convenience. Appreciating this helps prevent 'kangarooing' from analgesic to analgesic in a desperate search for some drug that will suit the patient better."[23]

Types of analgesics

There is no internationally agreed classification of analgesics. Some text books classify them according to their effectiveness in treating either mild or severe pain. Others classify them according to *where* they work – either at the site of the pain or on the brain. Pain relievers that work at the site of pain block the production of prostaglandins, which in turn prevents the stimulation of the nerve endings so no pain message is sent to the brain; those that work on the brain block the transmission of pain signals between brain cells and therefore interfere with the perception of pain.[24] Another approach is to talk about *narcotic* or *opioid* analgesics (those analgesics of natural or synthetic origin with actions like morphine) and

Table 4A-1
Sales figures and projections (in US$ millions) for pain management products in selected markets (1988-1995)

	1988	1989	1995
United States of America			
Total[1]	5000		7800
OTC[2]		2500	3610
Prescription[3]			4040
European Community[4]			
Total			7000
anti-inflammatory/ antipyretic analgesics		5700	
local anaesthetics			587
opioid analgesics			500
homoeopathic medicines			104
pain control devices			19
Germany			
Total			2067
OTC[5]		306	
UK			
Total			817
OTC[5]		215	
Italy			
Total			1231
OTC[5]		131	
France			
Total			1780
OTC[5]		71	
Spain			
Total			405
Benelux			
Total			374

Notes and sources:
1. These figures are the total for all pain management products, which includes prescription drugs, OTC drugs, devices and alternative therapies. From a report, Accelerated Growth in Pain Management Markets: *Forecasts of Pharmaceuticals, Devices and Alternative Treatments*, by the Market Intelligence Research Company (MIRC), reported in: Anon., "New publications", *Scrip*, No 1483, 26 Jan 1990, p4
2. OTC figure for 1989 is from a Euromonitor report, *Analgesics – The International Market 1991*, reported in: Anon., "OTC analgesic trend 'static'", *Scrip*, No 1587, 1 Feb 1991, p27; OTC figure for 1995 is from the MIRC report referred to above.
3. The prescription analgesics figure is from the MIRC report referred to above.
4. All the 1995 figures for the European Community and its member states are from a Frost and Sullivan report, *The European Market for Pain Management Products – Pharmaceuticals, Pain Control Devices & Alternative Medicines*, reported in: Anon., "European pain relief market set to rise", *Scrip*, No 1587, 1 Feb 1991, p27.
5. All the 1989 figures for the OTC market share by different countries is from the Euromonitor report referred to above.

non-narcotic or *non-opioid* analgesics (such as aspirin). Narcotic analgesics may produce drug dependence. They are used frequently and effectively to relieve severe pain, usually from internal organs, but also from other parts of the body. Non-opioid analgesics are used to relieve skin, muscle, joint, bone or tooth pains.[25] Still another classification divides pain killers into those that simply relieve pain and fever (antipyretics), and those that relieve pain, fever, *and* help to reduce inflammation.[26] The latter are usually described as non-steroidal anti-inflammatory drugs (NSAIDs) or, because aspirin is the prime NSAID, they are sometimes called aspirin-like drugs.[27]

The narcotic analgesics are generally subject to strict controls in most countries and are reserved for use in cases of severe pain such as after surgery, or in terminal cancer patients. There are fewer restraints on non-narcotic analgesics. In most countries, there are dozens on the market.

The WHO Essential Drugs List contains four non-opioid analgesics/antipyretics/NSAIDs. They are:
- *acetylsalicylic acid* (*aspirin*) – which has both analgesic and anti- inflammatory properties;
- *paracetamol* – an analgesic without significant anti-inflammatory properties;
- *ibuprofen* – an anti-inflammatory drug that is also effective as a pain killer; and
- *indomethacin* – an anti-inflammatory drug with analgesic properties.

Ibuprofen and indomethacin are included as examples of a *therapeutic group*, and other drugs in the same group may be substituted depending on cost and availability.[28] Such drugs could include other propionic acid derivatives for ibuprofen – naproxen, fenoprofen, ketoprofen, flurbiprofen, fenbufen, pirprofen, oxaprozin, indoprofen or tiaprofenic acid – and sulindac for indomethacin.

A Health Action International (HAI) survey published in 1986 found that three-quarters of the analgesics on the market in Africa, Indonesia, India, the Middle East and the Caribbean during 1985 should not be used – either because they contained potentially dangerous ingredients, were irrational or ineffective combinations, or were simply unnecessarily expensive when compared to equally effective alternatives on the market.[29]

A survey of drugs manufactured by German companies that were on the market in seven areas of the world in 1988 (Africa, Brazil, Central America, Colombia, India, Mexico, Philippines) found that 77% of the 81 analgesics were "inappropriate".[30] Drugs were classified as inappropriate because they were irrational combinations, efficacy data were lacking, safer alternatives were available, unsuitable dosage forms were used, or there was not enough active ingredient.

Combination products

One way companies try to distinguish their pain killers from a competitor's brand is to add extra ingredients and produce a combination drug. Popular combinations include:
- aspirin and/or paracetamol with codeine
- paracetamol or aspirin with dextropropoxyphene
- aspirin and/or paracetamol with caffeine
- paracetamol with pentazocine
- aspirin or paracetamol with vitamins
- aspirin and/or paracetamol with phenacetin
- aspirin or paracetamol with a pyrazolone derivative
- aspirin or paracetamol with a barbiturate.

As Table 4A-2 on the next page shows, a survey of 1988 prescribing guides from 13 regions of the world found that just under 40% of analgesics were combination products. By 1990, prescribing guides in Africa, the Caribbean, the Middle East and Pakistan indicated that one-third of the analgesics in those settings were combination products. This is despite years of standard independent advice that the use of combination analgesics offers no real advantage, can be harmful, and is certainly more costly. As one

Common analgesics

Opioid or narcotic analgesics
morphine
codeine
dextropropoxyphene
pentazocine
tramadol

Non-narcotic analgesics/antipyretics
aspirin*
paracetamol (acetaminophen)
dipyrone (metamizol)
glafenine
phenacetin
propyphenazone

Anti-inflammatories (NSAIDs)
aspirin
ibuprofen
indomethacin
mefenamic acid
diclofenac
ketoprofen
ketorolac
etodolac
naproxen
piroxicam
tiaprofenic acid

*Note: aspirin is classified as both a non-narcotic analgesic and an anti-inflammatory

textbook on clinical pharmacology says, "there is accumulating evidence that analgesic mixtures are more likely to produce renal [kidney] damage than single agents".[31]

The American Medical Association says that although mixtures of analgesics or of analgesics with other classes of drugs are among the most widely used pharmaceutical products, "relatively few well-controlled studies have been performed to determine their comparative effectiveness".[32] The British Medical Association concurs: "there is little evidence that preparations containing more than one analgesic are more effective than a single drug. A combined preparation may also combine the side effects of both classes of drug. For these reasons it is usually advisable to use a single ingredient preparation."[33]

According to the *British National Formulary*, "Compound analgesic preparations of, for example, aspirin, paracetamol, and codeine are *not* recommended. Single-ingredient preparations should be prescribed in preference because compound preparations rarely have any advantage and complicate the treatment of overdosage."[34] Thus, for example, although the combination of aspirin or paracetamol with an opioid such as codeine might be considered rational in the treatment of some types of moderate to severe pain, "it is advisable under most circumstances... to prescribe the two agents separately so that individual dose adjustments can be made".[35] In 1991, the Swiss regulatory authority, the IKS, announced that all combinations of analgesics with codeine would be made prescription-only. The IKS said that companies that wished to continue marketing these products as OTC preparations could do so by reformulating them without the codeine and filing an application for a modification to the product. It promised to process these applications without any further questions, provided no other ingredient was included to replace the codeine.[36]

Table 4A-2
Comparison of analgesics on the market in selected countries (1987-1990)

Country/ region	Year	Total no. of analgesics	No & % of drugs containing: dipyrone		other pyrazolones		barbiturates		vitamins		combinations	
			No.	%	No.	%	No.	%	No.	%	No.	%
Africa	1988	126	21	17	11	9	9	7	1	1	50	40
Brazil	1987-8	261	155	60	3	1	1	<1	34	13	135	52
Caribbean	1988	68	12	18	0		0		0		28	41
Hong Kong	1988	80	5	6	5	6	1	1	3	4	27	34
India	1988	73	18	25	3	4	2	3	0		48	66
Indonesia	1988	176	63	36	8	5	3	2	43	24	72	41
Malaysia &Singapore	1988	116	0		4	3	0		7	6	28	24
Mexico	1987	153	92	60	5	3	0		13	9	68	44
Middle East	1988	146	24	16	12	8	9	6	4	3	57	39
Pakistan	1987	205	26	13	4	2	4	2	3	2	60	29
Philippines	1988	179	6	3	1	1	0		1	1	17	10
South Africa	1988	135	8	6	2	2	5	4	2	2	98	73
Thailand	1988	133	28	21	3	2	0		2	2	28	21
Total	**1988**	**1851**	**458**	**25**	**61**	**3**	**34**	**2**	**113**	**6**	**716**	**39**
Africa	1989	121	18	15	9	7	1	1	2	2	42	35
Caribbean	1989	66	12	18	6	9	0		0		26	39
Middle East	1989	143	21	15	10	7	1	1	4	3	50	35
Pakistan	1988-9	177	21	12	2	1	1	1	3	2	49	28
Total	**1989**	**507**	**72**	**14**	**27**	**5**	**3**	**1**	**9**	**2**	**167**	**33**
Africa	1990	115	18	16	9	8	1	1	2	2	41	36
Caribbean	1990	66	12	18	6	9	0		0		26	39
Middle East	1990	141	21	15	10	7	1	1	5	4	52	37
Pakistan	1990	186	21	11	2	1	1	1	3	2	50	27
Total	**1990**	**508**	**72**	**14**	**27**	**5**	**3**	**1**	**10**	**2**	**169**	**33**
Totals	**1988-90**	**2866**	**602**	**21**	**115**	**4**	**40**	**1**	**132**	**5**	**1052**	**37**

Sources: Africa: *MIMS Africa* May 1988, July 1989, July 1990; Brazil: *DEF* 1987-88; Caribbean: *MIMS Caribbean* May 1988, Nov 1989, July 1990; Hong Kong: *HKIMS* April 1988; India: *MIMS India* Feb 1988; Indonesia: *IIMS* Feb 1988; Malaysia & Singapore: *DIMS* Feb 1988; Middle East: *MIMS Middle East* Apr 1988, Dec 1989, Jun 1990; Mexico: *DEF* 1987; Pakistan: *QIMP* 1987, 1988-89, 1990; Philippines: *PIMS* April 1988; South Africa: *MIMS* May 1988; Thailand: *TIMS* March 1988

Some specific combinations are particularly deprecated. The use of dextropropoxyphene in combination with either aspirin or paracetamol "should not be encouraged".[37] This is because "combinations of dextropropoxyphene with paracetamol and with aspirin can be more dangerous in overdose than aspirin or paracetamol on their own."[38] An overdose of dextropropoxyphene can cause respiratory depression, particularly in combination with alcohol; cardiac collapse and death follows rapidly.[39] For this reason, the drug has tragically become a popular and effective means of committing suicide. The widespread availability of analgesics containing dextropropoxyphene, as indicated in Table 4A-3, is a matter of some concern.

The inclusion of caffeine in pain killers "does not contribute to the analgesic or anti-inflammatory effect of the preparation and may possibly aggravate the gastric irritation caused by aspirin."[40] In most cases, the amount of caffeine contained in such combination products is not sufficient to enhance the analgesic effect of paracetamol or aspirin.[41] There is probably more caffeine in a cup of tea or coffee.[42] *Goodman and Gilman's The Pharmacological Basis of Therapeutics* notes that "there are few data to substantiate its efficacy for this purpose".[43] One recent (April 1991) study pointed out: "To date, to our knowledge, no single published study has definitively established the role of caffeine as an analgesic adjuvant".[44] The study itself offered some limited evidence that caffeine *was* useful as an analgesic adjuvant, at least for pain caused by a sore throat, over a period of two hours. Other recent studies found no significant difference between paracetamol and caffeine versus paracetamol in headache,[45] or between aspirin and caffeine versus aspirin in moderate postoperative oral surgery pain.[46] One study in Germany has found that there are strong associations of kidney disease with regular use of paracetamol-aspirin combinations, especially when taken jointly with caffeine.[47]

The combination of paracetamol with pentazocine is irrational. When given orally, pentazocine has "relatively weak and unpredictable analgesic activity". In both acute and chronic pain, other analgesics have been found to be equally or more effective and with fewer adverse effects than pentazocine.[48]

Barbiturates today have a very limited clinical use on their own and generally should be avoided because of dependence problems and the possibility of serious, often fatal, withdrawal effects.[49] Their use in combination with analgesics is totally unjustifiable.

Some countries have taken steps to remove combination analgesics. Analgesics in combination with alcohol, iron or vitamins have been banned in Bangladesh. Analgesics in combination with barbiturates have been withdrawn in Turkey. Analgesics in

Table 4A-3
Analgesics containing dextropropoxyphene in selected markets

Company	Brand name	Other ingreds.	Countries/regions where product was available
Darrow	Algafan	Pa	BR
Darrow	Algafan Comp.	Dc	BR
Boeh.Mann.	Algaphan	Pa	AF88;CA88,89,90; ME88,89,90
Concept	Anadex	Dp	IN
Arcana	Apa	Pa	HK
Fawns&McAllan	Capadex	Pa	HK
Roussel	Corbutyl	Pa	IN
SKF	Daprisal-P	As	IN
Lilly	Darvocet-N	Pa	AF88,89,90;CA88,89,90; ME88,89,90
PCW	Deprogesic	Cf,Pa	PK87,89,90
Remedica	Destirol	Pa	AF88,89,90;CA88,89,90; ME88,89,90
Jean-Marie	Dextropropoxy.	Ld	HK
Wilson's	Diagesic	Pa	PK87,89,90
Diba	Dibagesic	As	MX
Lilly	Distalgesic	Pa	AF88,89,90;CA88; ME88,89,90;SA
Lilly	Dologesic-32	Pa	HK,MS,PH
Pharmador	Dolorin	Cf,Co,Pa	SA
Al-Hikma	Dolostop	Pa	AF88,89,90;CA88; ME88,89,90
Al-Hikma	Dolostop Forte	Pa	AF88,89,90;CA88; ME88,89,90
Lilly	Doloxene Comp.	As,Cf	AF88,89,90;CA88, 89,90;HK; ME88,89,90;-PH;SA;TH
Lilly	Doloxene-A	As	BR
Nordmark	Dolo-Neurotrat	Vi	MS
Synco	Dolpocetmol	Pa	HK
Covan	Doxyfene	Pa	SA
Silanes	Espasmo-Qual	Dp,Dc	MX
Continentales	Fardolina Comp.	Dp	MX
Lepetit	Femidol	As,Cp,Pa,Cf	AF88,89;ME88,89,90
Mer-Nat.	Lentogesic	Pi,Gt	SA
Medochemie	Medonol	Pa	AF88,89,90;CA88, 89,90;ME88,89,90
DuPont	Neo-Percodan	Pa	MX
Cipla	Norgesic	Pa	IN
Pharmador	Paprox	Pa	SA
Protea	Paradex	Pa	MS
JagsonPal	Parvon/(-N)	Dz,Pa	IN
JagsonPal	Parvon-P	Pa	IN
JagsonPal	Parvon-Spas	Di,Dz,Pa	IN
Wockhardt	Proxyvon	Pa	IN
Silanes	Qual	Pa	MX
Wockhardt	Spasmo-Proxyvon	Dc,Pa	IN
Ranbaxy	Sudhinol	Pa	IN
Restan	Synap Forte	Cf,Dh,Pa	SA
Wallace	Walagesic	Dz,Pa	IN
Wyeth	Wygesic	Pa	IN

Contents key:
As=aspirin, Cf=caffeine; Co=codeine; Cp=chlorpheniramine; Dc=dicyclomine; Dh=diphenhydramine; Di=dipipanone; Dp=dipyrone; Dz=diazepam; Gt=glutamine; Ld=lidocaine; Pa=paracetamol; Pi=pemoline. Vi=vitamins

Country/region key and sources:
AF=AFRICA: *MIMS Africa*: May 1988, July 1989, July 1990; BR=BRAZIL: *DEF*: 1987-88; CA=CARIBBEAN: *MIMS Caribbean*: May 1988, November 1989, July 1990; HK=HONG KONG: *HKIMS*: April 1988; IN=INDIA: *MIMS India*: Feb 1988; MS=MALAYSIA & SINGAPORE: *DIMS*: Feb 1988; ME=MIDDLE EAST: *MIMS Middle East*: April 1988, December 1989, June 1990; MX=MEXICO: *DEF*: 1987; PK=PAKISTAN: *QIMP*: 1987, 1988-89, 1990; PH=PHILIPPINES: *PIMS*: April 1988; SA=SOUTH AFRICA: *MIMS*: May 1988; TH=THAILAND: *TIMS*: March 1988

Aspirin: preventing the headache of heart ache

At the end of January 1988, Reckitt and Colman shares began to soar on the London Stock Market; across the Atlantic ocean, a similar boom hit the shares of Sterling and Bristol Myers. All three companies are major manufacturers of aspirin. They were benefitting from a surprise announcement in the *New England Journal of Medicine*, that an aspirin every other day could reduce the risk of a healthy person having a heart attack by about 50%. The claim was based upon the preliminary findings of a study of 22,000 male physicians in the USA, half of whom were taking aspirin, the other half were receiving a placebo. The researchers halted the trial two years earlier than planned in order to release the results "to help save lives". Not surprisingly, the news made headlines around the world. *Newsweek*, for example, ran a cover story about the findings. Some concern was initially expressed about the way the information was made public without drawing clear attention to the possibility that although heart attacks might decrease, haemorrhagic (bleeding) strokes could increase, due to aspirin's ability to thin the blood. (That ability means that aspirin *is* valuable in the treatment of strokes caused by blood clots, where it has been shown to reduce the risk of recurrent stroke by about 25-30%). The US Food and Drug Administration asked aspirin manufacturers not to begin to claim that the drug prevents heart attacks. The final report of the physician's study was published by the *New England Journal of Medicine* in July 1989. The overall reduction in risk of heart attack was found to be 44%; however, the reduction in risk was apparent only among those who were 50 years of age and older and the study failed to find a significant reduction in risk of death from *all* cardiovascular causes. Another study, the second International Study of Infarct Survival (ISIS-2) – which followed 17,000 patients in 16 countries who had just had a heart attack and who were treated with either aspirin, a blood clot dissolving drug called streptokinase, both drugs or a placebo – found that an aspirin a day for a month reduced the risk of death by 23%, streptokinase alone by 25%, and both drugs by at least 34%. An observational study of nearly 88,000 female nurses in the USA, reported in 1991, found some evidence that regular aspirin use might be associated with reduced risk of heart attack, but was unable to determine whether there was a significant reduction in the risk of cardiovascular death.

Research is continuing into the use of aspirin in the prevention and treatment of cardiovascular disease. Because of aspirin's well-documented adverse effects, the use of the drug without medical supervision in an attempt to prevent heart attacks is foolhardy and likely to cause complications.

Sources: Steering Committee of the Physicians' Health Study Research Group, "Preliminary report: Findings from the aspirin component of the ongoing Physicians' Health Study", *New England Journal of Medicine*, Vol 318, No 4, 28 Jan 1988, pp262-4; Relman, A.S., "Aspirin for the primary prevention of myocardial infarction", *New England Journal of Medicine*, Vol 318, No 4, 28 Jan 1988, pp245-6; Steering Committee of the Physicians' Health Study Research Group, "Final report on the aspirin component of the ongoing Physicians' Health Study", *New England Journal of Medicine*, Vol 321, No 3, 20 Jul 1989, pp129-35; Fuster, V., Cohen, M. and Halperin, J., "Aspirin in the prevention of coronary disease", *New England Journal of Medicine*, Vol 321, No 3, 20 Jul 1989, pp183-5; ISIS-2 Collaborative Group, "Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2", *Lancet*, No 8607, 13 Aug 1988, pp349-60; Hershey, L.A., "Stroke prevention in women: role of aspirin versus ticlopidine", *American Journal of Medicine*, Vol 91, No 3, Sep 1991, pp288-92; Leppard, D., "Aspirin: a headache for science", *The Sunday Times* (London), 31 Jan 1988, pA10; Clark, M., "What you should know about heart attacks", *Newsweek*, 8 Feb 1988, pp42-6; Kingman, S., "Will an aspirin a day keep the doctor away?", *New Scientist*, 11 Feb 1988, p26; Anon., "FDA checks aspirin claims", *New Scientist*, 10 Mar 1988; Anon., "Aspirin cuts deaths after heart attacks", *New Scientist*, 7 Apr 1988, p22; Anon., "Aspirin prevents first MI in women?", *Scrip*, No 1639, 2 Aug 1991, p25; Graedon, J. and Graedon, T., *Graedon's Best Medicine. from herbal remedies to high-tech Rx breakthrough*, New York, Bantam Books, 1991, p79

combination with vitamins have been disapproved in the Philippines as an irrational combination, and have been prohibited for manufacture, sale and import in India.[50]

Aspirin

Most expert opinion agrees that, for the treatment of simple, intermittent pain – toothache, headache, occasional backache – aspirin is the "analgesic of choice".[51] The *Textbook of Pain* says: "In terms of effectiveness, it is difficult to improve on aspirin. No currently available drugs... have been shown to be more than marginally better."[52] So popular is aspirin that more than 40 billion aspirin tablets a year are consumed in the USA alone.[53]

Aspirin does have its disadvantages. It probably should be avoided by people with uncontrolled high blood pressure, or with a tendency to bleed. Also, people with asthma, ulcers or sensitive stomachs, or anyone with an allergy to aspirin-like drugs should not use aspirin.[54] Aspirin is *not* recommended for children under 12, because of its association with the development of Reye's Syndrome, a serious, potentially life-threatening disease in children with viral infections.[55] The US Surgeon General warned against the use of aspirin or related salicylates for children suffering from chicken pox or influenza in 1982; similar warnings were issued in the UK in 1986, and all aspirin formulations for children were withdrawn from the market.[56] In Peru in 1990 there were at least five anti-flu products especially for children that contained aspirin.[57] In March 1990, the Australian

Analgesics and alcohol: a bad mix

In Spain, a 1991 television advertisement shows a couple arriving home from a party. One complains of a headache, the other of stomach upset; both take Alka-Seltzer – an effervescent preparation of aspirin, calcium phosphate, sodium bicarbonate and citric acid. Similar ads have been used in the UK, while in the USA, Alka-Seltzer preparations are labelled as being useful for "upset stomach with headache from overindulgence". In Barranquilla, Colombia, in 1991, packets of Alka-Seltzer were included in the stock of mini-bars in a leading five-star hotel, while a complimentary packet of two of Bayer's brand of effervescent aspirin, Aspirina, was left on the pillow for hotel guests each evening. The message on the Aspirina packet was: "sleep well without pain... with Aspirina, which does not irritate your stomach." ["Buenas noches sin dolor... con Aspirina, qué no irritata su estómago!"]

As Alain Po points out, "the common practice of using aspirin to relieve 'hangover' headache should be questioned". Aspirin *does* irritate the stomach, causes gastric bleeding and pain and may cause ulcers. Alcohol has a similar effect; combining the two simply increases the risk.

Paracetamol also has risks. The British Medical Association says that "large doses of paracetamol may be toxic if you are a regular consumer of even moderate amounts of alcohol". There is also some evidence to suggest that alcohol may increase the likelihood of liver damage by smaller doses of paracetamol.

Ibuprofen is also not a good drug to combine with alcohol. Unlike aspirin, ibuprofen rarely causes bleeding in the stomach; however, like aspirin, with alcohol, the risk of stomach disorders with ibuprofen increases.

Sources: Po, A.L.W., *Non-Prescription Drugs*, (2nd edn), Oxford, Blackwell Scientific, 1990, pp520; Figueras, A., Juan, J., et al, "Misuse of aspirin for abdominal discomfort", *Lancet*, Vol 338, No 8765, 24 Aug 1991, pp506-7; Diamond, J., "They'll never swallow that", *Sunday Times Magazine*, 17 May 1987, pp82-4; Henry, J. (ed.), *The British Medical Association Guide to Medicines & Drugs*, London, Dorling Kindersley, (2nd edn) 1991, pp195, 286, 332

company, Nicholas, promoted its brand of aspirin tablets, Aspro, in East Africa for children as young as one year "for headache, toothache, earache, fever, colds and flu".[58]

Paracetamol

If it is not advisable to use aspirin, the next best choice is paracetamol (also known as acetaminophen in many countries), "probably a little less effective", but "a very well-tolerated alternative."[59] Paracetamol "is less irritant to the stomach."[60] However, regular and prolonged use of paracetamol may cause liver and kidney damage, and an overdose may cause serious liver damage which can be fatal.[61] In the USA, in the 10-year period from 1976 to 1985, over 11,000 cases of suspected paracetamol overdose were reported.[62] Paracetamol poisoning is estimated to constitute 5% of the total number of drug poisonings in the USA and the UK.[63] In 1986, 200 people in the UK overdosed on paracetamol.[64] As little as 20-30 tablets (10-15g) of paracetamol is enough to cause potentially fatal liver damage.[65]

The best advice is to use paracetamol, or *any* analgesic, sparingly. Two researchers investigating the possible risk of kidney damage with paracetamol concluded that "it is naive to think that this or any drug is safe in all circumstances for all uses in all patients. It seems prudent to discourage the unnecessary daily use of acetaminophen."[66]

A doctor at Vanderbilt University advises that "caution in the use of acetaminophen in certain situations would appear to be prudent. Its use should be avoided in patients with any active hepatic processes and minimised in habitual consumers of alcohol."[67]

Ibuprofen

NSAIDs such as ibuprofen are generally more expensive than aspirin or paracetamol, and they are not necessarily *more* effective. However, a limited number of studies have indicated that ibuprofen is at least as effective or more effective than aspirin. A significant benefit of ibuprofen is that it tends to have a low incidence of adverse effects and is generally better tolerated than aspirin.[68] However, it is not recommended for use by pregnant women or during breastfeeding.[69] The US FDA requires that labelling for 200mg ibuprofen tablets carries a warning that "it is especially important not to use ibuprofen during the last three months of pregnancy unless specifically directed to do so by a doctor because it may cause problems in the unborn child or complications during delivery".[70] It is not recommended for children under one year of age.[71]

Tramadol

Tramadol first appeared in Germany in 1977, launched by the German company, Grünenthal. It is an opioid analgesic which appears to have less likelihood of causing dependency than morphine and less respiratory depression and sedation than some of the

A combination drug that copes with paracetamol overdose

In 1975, Dr André McLean, a professor of toxicology at University College Hospital in London, suggested that an antidote for paracetamol overdose – methionine – should be added to paracetamol tablets. One reason for this is that unless the antidote is given within 10-12 hours, it is not effective. The British Technology Group and Sterling Winthrop (one of the major manufacturers of paracetamol) jointly developed such a product (Pameton) which was given a product license in the UK in 1983, and went on general sale in 1986. One drawback to Pameton is its higher price: in 1991, a tablet containing 500mg of paracetamol plus 250mg of methionine cost about 9 times a generic 500mg tablet of paracetamol. However, Pameton is considerably cheaper, both in financial and human terms, than the additional treatment should an overdose with plain paracetamol occur.

When the product came onto the market in 1986, Sterling Winthrop gave it little or no publicity. A spokesperson at the company, Dennis Boyles, agreed that the company had been rather discreet about the drug. He told a *Sunday Times* reporter, "We probably should be giving it more publicity, and it would be a reasonable thing to have in a house where there are children." One UK pharmacist suggested that the reason for the company's modesty was that promoting the drug might convey to the public the idea that paracetamol is unsafe, something that would undoubtedly affect the company's heavy selling pain killers like Panadol which contain paracetamol.

If an overdose of paracetamol does occur, the usual treatment (within 10-12 hours) is methionine tablets, or within about 15-16 hours, intravenous acetylcysteine or liquid acetylcysteine or as a tablet, where these are available.

Sources: BMA and the Royal Pharmaceutical Society of Great Britain, *British National Formulary*, London, BMA and The Pharmaceutical Press, No 22, Sep 1991, p18; Diamond, J., "They'll never swallow that", *Sunday Times Magazine*, 17 May 1987, pp82-4; Anon., "Cold shoulder for 'safe' paracetamol", *New Scientist*, 18 Dec 1986; McLean, A.E.M., "Why do patients still die from paracetamol poisoning?", *British Medical Journal*, Vol 293, 1 Nov 1986, p1172; Gilman, A.G., Rall, T.W., Nies, A.S., and Taylor, P., *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, New York, Pergamon Press, (8th edn) 1990, p658; Dukes, M.N.G., (ed.), *Side Effects of Drugs Annual 11*, Amsterdam, Elsevier, 1987, pp80-1

other opioid drugs.[72] The product is on the market in Japan, several other Asian countries and in Latin American countries, and applications for licences are pending in several European countries.[73] However, there is too little clinical data available to determine the role of the drug in pain therapy.

Glafenine

Another analgesic that is prevalent in many markets in developing countries is glafenine, also marketed by a German company Hoechst or its French subsidiary, Roussel. Global sales of the drug in 1984 amounted to some $30 million, making it one of Hoechst's top 10 drugs. In France, it was the best selling prescription analgesic in 1986.[74] By 1990, sales in France had reached some 4.2 million packs, and the product was on the market in more than 70 countries worldwide.[75] Nonetheless, there is little information in the international literature about the efficacy of the drug in comparison to other analgesics.

However, it does feature in regular reports about adverse effects. In France, glafenine is second only to phenacetin as the commonest cause of drug-induced kidney damage.[76] Liver damage has also "repeatedly been described in patients taking glafenine", and the damage is characterised by a high prevalence of jaundice and a high fatality rate.[77] In 1980, 1981 and 1982 more adverse drug reaction (ADR) reports in France involved glafenine than any other drug; between 1 April 1980 and 31 October 1982, the French authorities received 734 reports of reactions possibly caused by glafenine.[78] In the Netherlands, glafenine has been the most frequently reported cause of drug-induced anaphylaxis (allergic reaction which can lead to life-threatening shock) since its registration in 1967; in 1980-84, for example, 121 cases of anaphylaxis to glafenine were reported to the Netherlands Centre for Monitoring of Adverse Reactions to Drugs.[79] Worldwide, 14 deaths have been attributed to the drug.[80]

Largely on the basis of the information from the Netherlands, the German Federal Health Office began to look closely at the drug in the early 1980s. Before the process had gone very far, Hoechst quietly withdrew the drug from the German market in 1983. Hoechst's headquarters claimed that the withdrawal of glafenine was a pure marketing decision.[81]

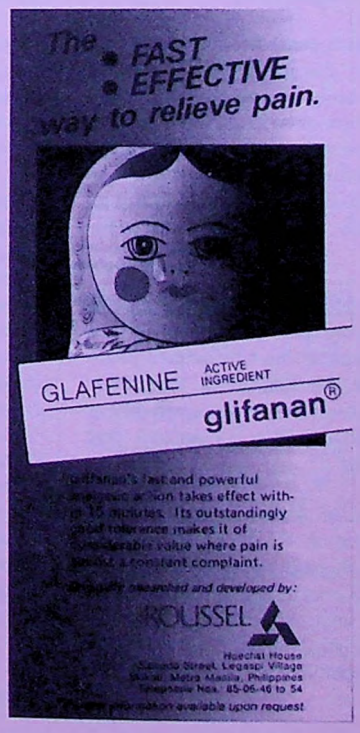
In 1985, Hoechst/Roussel promoted its brand of glafenine, Glifanan, as "tomorrow's analgesic" in an advertisement in the *East African Medical Journal*. It described the drug as "the ideal pure analgesic: potent, yet safe, and flexible". In 1990, in the Philippines, the company was promoting glafenine as a drug with "outstandingly good tolerance".[82]

On 1 January 1991, Roussel withdrew glafenine from the Belgian market at the request of the Belgian Secretary of State for Health, Roger Délizée.

Table 4A-4
Analgesics containing glafenine in selected markets

Company	Brand name	Other ingreds.	Countries/regions with product available
Roussel	Adalgur*	Th,Mp	AF88,89,90;CA88,89,90; ME88,89,90
Biomedis	Biofenin		ID
Pyridam	Citofen		ID
Meprofarm	Fenal		ID
Terramedic	Flanin		PH
Unilab	Glafenine		PH
Siam B.	Glafine		TH
United Amer.	Glafine		PH
Pharos	Glaphen		ID
Roussel/Hoechst	Glifanan*		AF88,89,90;BR; CA88;89,90;ID;MS; ME88,89, 90;PH;TH
Sarsa/Hoechst	Glifarelax*	Th	BR
Pyridam	Neuro-Citofen	Vi	ID
Biomedis	Revalan		PH
Biomedis	Skelan Forte	Cs,Pk	PH

*withdrawn, May 1992
Contents key:
Cs=carisoprodol; Mp=meprobamate; Pk=phenylbutazone; Th=thiocolchicoside; Vi=vitamins
Country/region key and sources:
AF=AFRICA: *MIMS Africa*: May 1988, July 1989, July 1990; BR=BRAZIL: *DEF*: 1987-88; CA=CARIBBEAN: *MIMS Caribbean*: May 1988, November 1989, July 1990, ID=INDONESIA: *IIMS*: Feb 1988; MS=MALAYSIA & SINGAPORE: *DIMS*: Feb 1988; ME=MIDDLE EAST: *MIMS Middle East*: April 1988, December 1989, June 1990; PH=PHILIPPINES: *PIMS*: April 1988; TH=THAILAND: *TIMS*: March 1988



This Roussel/Hoest advertisement from the Phillipines in 1988 emphasises Glifanan's "outstandingly good tolerance". In 1992, the drug was withdrawn worldwide because of safety concerns – concerns that had been evident for more than 10 years.

Mr Délizée said the reason for the withdrawal was the drug's adverse effects, which included two deaths in patients in Belgium who took the drug without medical advice.[83] In early 1992, the European Committee for Proprietary Medicinal Products (CPMP) advised that marketing approvals for glafenine should be withdrawn because of the high risk of anaphylactic shock.[84] It was subsequently withdrawn or suspended in Spain, France, the Netherlands, Italy and Portugal,[85] and in May 1992, Roussel announced a global withdrawal of the drug, although other manufacturers may still be producing it.[86]

Phenacetin

Phenacetin was first introduced into therapy in 1887 and is structurally very similar to paracetamol, which is a metabolite of phenacetin. Not surprisingly, it has a similar analgesic affect as paracetamol, but it is now generally considered too toxic for regular use. It has been identified as a carcinogen, and its prolonged use has been strongly correlated with a high incidence of kidney disease and anaemia.[87]

A major 20-year epidemiological study of abuse of analgesics conducted in Switzerland from 1968 to 1987 found that regular use of analgesics containing phenacetin increased the risk of hypertension and increased the risk of death from cardiovascular disease, cancer, or kidney disease. The study documented 74 deaths among 623 female phenacetin users compared to only 27 deaths in 621 matched controls, a relative risk of 2.2. Analysis of the relative risk of death due to kidney disease produced a figure of 16.1.[88]

A less reliable case-control study of 554 adults with newly diagnosed kidney disease in the USA found that daily users of any analgesic (phenacetin, paracetamol or aspirin) were about twice as likely to have kidney disease than those who used analgesics infrequently. The risk of kidney disease was highest in daily users of phenacetin (odds ratio, 5.11), although it was also a risk in daily use of paracetamol (odds ratio, 3.21).[89]

An editorial in the *New England Journal of Medicine*, commenting on the Swiss study, pointed out the public health implications of leaving a product like phenacetin on the market. It said, "the removal of phenacetin, both as a single agent and as part of a compound, is advisable in countries that still allow use of the drug".[90]

A US FDA panel concluded as far back as 1977 that phenacetin "is not safe for OTC use because of the high potential for abuse, the high potential for harm to the kidney and the lack of compensating benefits of the drug". The panel also suggested that it "should be removed from analgesic compounds".[91] It was withdrawn in the USA and prohibited for export in 1983.[92]

Table 4A-5
Analgesics containing phenacetin in selected markets

Company	Brand name	Other ingredients	Countries/regions where product was available
Teuto	Analgin	As,Cf,Bt	BR
PPP	Aspagin	As	PK87
Vernleigh	Codaspasol	As,Co	SA
Vernleigh	Contradol	As,Co, Cf,Pb,Pl	SA
Pfizer	Coryban	As,Cf, Cp,Pf,Vi	PK87,89,90
AFD	Maldrine	Bb,Pc	PK87
Riker	Norgesic Forte	As,Cf,Or	CA88,89,90
Vernleigh	Tricodein	As,Co	SA

Contents key:
As=aspirin; Bb=butobarbitone; Bt=butalbital butylbromide; Cf=caffeine; Co=codeine; Cp=chlorpheniramine; Or=orphenadrine; Pb=phenobarbitone; Pc=phenylsemicarbazide; Pl=phenylpropanolamine; Pl=phenolphthalein; Vi=vitamins
Country/region key and sources:
BR=BRAZIL: *DEF*: 1987-88; CA=CARIBBEAN: *MIMS Caribbean*: May 1988, November 1989, July 1990; PK=PAKISTAN: *QIMP*: 1987, 1988-89, 1990; SA=SOUTH AFRICA: *MIMS*: May 1988

Phenacetin has also been banned or withdrawn in Canada, Chile, Cyprus, Denmark, Egypt, Finland, Germany, India, Israel, Italy, Japan, Malaysia, Mauritius, Nepal, The Netherlands, New Zealand, Nigeria, Norway, The Philippines, Rwanda, Saudi Arabia, Surinam, Sweden, Thailand, Turkey, the UK, and Yemen.[93]

Despite this action, a few analgesics containing phenacetin can still be found. As Table 4A-5 shows, products containing phenacetin were on the market in the Caribbean and Pakistan in 1988, 1989 and 1990; and in Brazil and South Africa in 1988.

Pyrazolones

The pyrazolones also date from the late 19th century. Most have now disappeared off the market because of their potential for causing agranulocytosis (a potentially fatal condition in which the white blood cell count is reduced, leaving the victim susceptible to many diseases).[94] A few, however, still remain; among them, phenylbutazone, propyphenazone and dipyrone, as well as a more recent addition, apazone.

Phenylbutazone is now usually reserved for use in treating the pain of particular types of arthritis (see the section on NSAIDs for more information). Apazone is a new agent that is also being tried in some forms of arthritis. Propyphenazone and dipyrone are the agents that most regularly appear in analgesics, and of these, the most popular is dipyrone.

The major manufacturer of dipyrone, the German company Hoechst, relies heavily on the product. In

1987, Hoechst's two dipyrone products – Novalgin and Baralgin – accounted for more than 5% of the company's total world drug sales.[95] In 1991, Novalgin alone had global sales of some $125 million and contributed 2.3% of the company's total sales.[96] As Table 4A-2 indicated (see page 72), in 1987-88, dipyrone featured in 25% of the analgesics on the market in 13 areas of the world, while in 1990, in Africa, the Caribbean, the Middle East and Pakistan, one out of every seven analgesics contained dipyrone.

There is little if any justification for the use of dipyrone or any of the other pyrazolones for the treatment of acute pain. According to the *Martindale* guide to medicines, because of the risk of agranulocytosis the use of dipyrone "is justified only in serious or life-threatening situations where no alternative antipyretic is available or suitable".[97] A major textbook on clinical pharmacology notes that dipyrone is "notorious" in causing agranulocytosis and "need never be used, as there are adequate substitutes."[98]

A further problem with dipyrone is its propensity to cause anaphylactic shock (serious, widespread allergic reaction). The importance of shock has been underestimated until recently. According to a German textbook on clinical pharmacology, the risk of dipyrone-induced shock is 1 to 50,000 for oral use, and could be 1 to 5,000 for injections.[99]

As long ago as 1973, the American Medical Association's *Drug Evaluations* said that dipyrone's "use as a general analgesic, antiarthritic or routine antipyretic cannot be condoned".[100] The 1977 edition stated that the drug had become "obsolete in the US",[101] and any mention of it has disappeared from subsequent editions. The US FDA withdrew it from the market and prohibited it for export in 1977.[102]

Slowly, action is being taken in other countries to remove dipyrone and other pyrazolones from the market. Eighty analgesic preparations containing a pyrazolone in combination with another active compound were withdrawn from sale in the Federal Republic of Germany in 1982 (however some products containing dipyrone alone and in combination were allowed to remain); all combination products containing dipyrone were taken off the market in Israel in 1983; combinations of pyrazolones with antihistamines, vasoconstrictors, decongestants, muscle relaxants, antibiotics or vitamins are prohibited in Mexico; several combination products containing pyrazolones are not approved in the Philippines.[103]

Dipyrone is prohibited for importation into Australia or Singapore; withdrawn or banned in Denmark, Norway and Sweden; is severely restricted in Bangladesh, Egypt, Germany, Greece, Israel, Italy, Peru, the Philippines, and Venezuela; not accepted for use in paediatric preparations in Mexico.[104]

Propyphenazone has been banned or withdrawn in Ireland and Turkey.[105]

All pyrazolones have been severely restricted in Germany, Greece, Japan and Saudi Arabia.[106]

[See also the sections on *Dipyrone* and *NSAIDs*.]

Time for action

The misuse of analgesics can have serious and sometimes fatal side effects. Analgesic-associated kidney disease or kidney failure is a global problem. Where reliable studies have been done, a significant proportion of patients undergoing kidney replacement or dialysis can be linked to the use of analgesics. In Australia in 1987, the figure was 13%; in Germany in 1986, it was 16.8%; in Belgium in 1988, it was 18%.[107] To assume that simply because a product is available over the counter it is "safe" is a serious mistake.

The bewildering array of analgesics on the market in many countries, all being promoted as being more effective, faster acting, or safer for the treatment of pain, only complicates matters. For many of them, as was noted earlier, no proof can be found for the claims. For some of them, the evidence is clear that the risks outweigh any supposed benefits. The time has come to introduce a more rational approach to treating pain.

Recommendations for action

1. All analgesics should be limited to single ingredient preparations (with the exception of buffered aspirin, or of paracetamol combinations with a methonine antidote).
2. All analgesics containing dextropropoxyphene, glafenine, phenacetin or pyrazolone derivatives should be removed from the market immediately.
3. All analgesics should be clearly labelled with the generic name of the product as well as maximum dosage limits, particularly in the case of paracetamol.

Notes and references:

1. McLeod, D.C., "An analgesic for nonprescription pain reliever promotions", *Drug Intelligence and Clinical Pharmacy*, Vol 22, Jun 1988, p503
2. Grichnik, K.P. and Ferrante, F.M., "The difference between acute and chronic pain", *Mount Sinai Journal of Medicine*, Vol 58, No 3, May 1991, pp217-20
3. Holland, A.J.A., Jackson, S.H.D. and Turner, P., "A survey of analgesic drug utilization within and between clinical units in a health district", *International Journal of Clinical Pharmacology, Therapy and Toxicology*, Vol 26, No 9, 1988, pp465-7
4. Greenwald, H.P., "Interethnic differences in pain perception", *Pain*, Vol 44, 1991, pp157-63
5. Po, A.L.W., *Non-Prescription Drugs*, Oxford, Blackwell Scientific, (2nd edn) 1990, p9
6. According to a 1989 report, *Accelerated Growth in Pain Management Markets, Forecasts of Pharmaceuticals, Devices and Alternative Treatments*, by the Market Intelligence Research Company, reported in: Anon., "New Publications", *Scrip*, No 1483, 26 Jan 1990, p4
7. According to a 1991 Frost and Sullivan report, *The European Market for Pain Management Products – Pharmaceuticals, Pain Control Devices & Alternative Medicines*, reported in: Anon., "European pain relief market set to rise", *Scrip*, No 1587, 1 Feb 1991, p27
8. Laurence, D.R. and Bennett, P.N., *Clinical Pharmacology*, Edinburgh, Churchill Livingstone, (6th edn), 1987, p301
9. Ibid, p302
10. Acs, G. and Drazner, E., "The incidence of postoperative pain and analgesic usage in children", *Journal of Dentistry for Children*, Jan-Feb 1992, pp48-52
11. Liebeskind, J.C., "Pain *can* kill", *Pain*, Vol 44, 1991, pp3-4
12. Grichnik and Ferrante, op cit, pp217-20
13. Laurence and Bennett, op cit, p303
14. Gaukroger, P.B., "Paediatric analgesia: Which drug? Which dose?", *Drugs*, Vol 41, No 1, 1991, pp52-9
15. Maunuksela, E-L. and Olkkola, K.T., "Pediatric pain management", *International Anesthesiology Clinics*, Vol 29, No 2, May 1991, pp37-55 (However, pain resulting from chronic diseases or surgery does demand sensitive and often prophylactic therapy as children typically do not request analgesics as adults do.)
16. Grichnik and Ferrante, op cit, pp217-20
17. Lebovits, A.H., "Chronic pain: the multidisciplinary approach", *International Anesthesiology Clinics*, Vol 29, No 1, 1991, pp1-7
18. Ibid; Turk, D.C. and Rudy, T.E., "Neglected topics in the treatment of chronic pain patients – relapse, noncompliance, and adherence enhancement", *Pain*, Vol 44, 1991, pp5-28
19. Parish, P., *Medicines: A Guide for Everybody*, (6th edn, revised), London, Penguin, 1989, p137
20. Katz, J. and Melzack, R., "Auricular transcutaneous electrical nerve stimulation (TENS) reduces phantom limb pain", *Journal of Pain and Symptom Management*, Vol 6, No 2, Feb 1991, pp73-83
21. Beecher, H.K., "The powerful placebo", *Journal of the American Medical Association*, Vol 159, 1955, pp1602-6
22. Scarani, G., Beghi, E. and Tognoni, G., "Pharmacological treatment of a primary headache: analysis of current practice from a drug utilization study", *Headache*, Vol 27, Jun 1987, pp345-50
23. Laurence and Bennett, op cit, p307
24. Henry, J. (ed.), *The British Medical Association Guide to Medicines & Drugs*, London, Dorling Kindersley, (2nd edn) 1991, p77
25. Parish, op cit, p188
26. Wall, P.D. and Melzack, R., (eds), *Textbook of Pain*, London, Churchill Livingstone, 1984, p505
27. Gilman, A.G., Rall, T.W., Nies, A.S., and Taylor, P. (eds), *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, New York, Pergamon Press, (8th edn) 1990, p638
28. WHO, "WHO Model List: revised in November 1991", *WHO Drug Information*, Vol 5, No 4, 1991, p182
29. Chetley, A. and Gilbert, D., *Problem Drugs*, The Hague/Penang, Health Action International, 1986
30. Hartog, R. and Schulte-Sasse, H., *German and Swiss drug supplies to the Third World*, Amsterdam/Zurich/Lausanne/Bielefeld, HAI-Europe/Berne Declaration Group/ BUKO Pharma-Kampagne, 1990, p32
31. Gillies, H.C., Rogers, H.J., Spector, R.G. and Trounce, J.R., *A Textbook of Clinical Pharmacology*, (2nd edn), London, Hodder and Stoughton, 1986, p308
32. AMA, *Drug Evaluations*, Philadelphia, W.B. Saunders Co., (6th edn) 1986, p76
33. Henry, op cit, p77
34. BMA and the Royal Pharmaceutical Society of Great Britain, *British National Formulary*, London, BMA and The Pharmaceutical Press, No 22, Sep 1991, p161
35. Analgesic Guidelines Sub-Committee, Victorian Drug Usage Advisory Committee, *Analgesic Guidelines*, (1st edn), Toorak, Victorian Medical Postgraduate Foundation, 1988, p22
36. Anon., "New Swiss analgesic prescribing rules", *Scrip*, No 1607, 12 Apr 1991, p9
37. Analgesic Guidelines Sub-Committee, op cit, p18
38. Parish, op cit, p192
39. BMA and the Royal Pharmaceutical Society of Great Britain, op cit, p18
40. Ibid, p161
41. Laurence and Bennett, op cit, p307
42. Po, op cit, p535
43. Gilman, et al, p629
44. Schachtel, B.P., Fillingim, J.M., et al, "Caffeine as an analgesic adjuvant: a double-blind study comparing aspirin with caffeine to aspirin and placebo in patients with sore throat", *Archives of Internal Medicine*, Vol 151, Apr 1991, pp733-7
45. Ward, N., Whitney, C., Avery, D. and Dunner, D., "The analgesic effects of caffeine in headache", *Pain*, Vol 44, 1991, pp151-5
46. Forbes, J.A., Jones, K.F., et al, "Evaluation of aspirin, caffeine, and their combination in postoperative oral surgery pain", *Pharmacotherapy*, Vol 10, No 6, 1990, pp387-93
47. Bennett, W.M. and DeBroe, M.E., "Analgesic nephropathy – a preventable disease", *New England Journal of Medicine*, Vol 320, No 19, 11 May 1989, pp1269-71
48. Hoskin, P.J. and Hanks, G.W., "Opioid agonist-antagonist drugs in acute and chronic pain states", *Drugs*, Vol 41, No 3, 1991, pp326-44
49. BMA and the Royal Pharmaceutical Society of Great Britain, op cit, p132
50. United Nations, *Consolidated List of Products Whose Consumption and/or Sale Have Been Banned, Withdrawn, Severely Restricted or Not Approved by Governments*, 2nd issue, Doc No ST/ESA/192, New York, 1987, pp105, 107, 118
51. BMA and the Royal Pharmaceutical Society of Great Britain, p159
52. Wall and Melzack, op cit, p507
53. Jones, M.P. and Schubert, M.L., "What do you recommend for prophylaxis in an elderly woman with arthritis requinng NSAIDs for control?", American Journal of Gastroenterology, Vol 86, No 3, 1991, pp264-6
54. Graedon, J. and Graedon, T., *Graedon's Best Medicine: from herbal remedies to high-tech Rx breakthrough*, New York, Bantam Books, 1991, p79
55. BMA and the Royal Pharmaceutical Society of Great Britain, op cit, p159
56. Lesser, F., "Aspirin: the slow gestation of a warning", *New Scientist*, 19 Jun 1986, p23
57. Lopez, R. and Kroeger, A. (eds), *Morbilidad y Medicamentos en Perú y Bolivia*, Lima/Heidelberg/Chimbote, Universidad Peruana Cayetano Heredia/Universidad de Heidelberg/Acción para la Salud, 1990, p146
58. MaLAM letter to Nicholas, March 1990
59. Wall and Melzack (eds), op cit, p507
60. BMA and the Royal Pharmaceutical Society of Great Britain, op cit, p159
61. Parish, op cit, p195
62. Nelson, S.D., "Molecular mechanisms of the hepatotoxicity caused by acetaminophen", *Seminars in Liver Disease*, Vol 10, No 4, 1990, pp267-78
63. Levy, M., "Adverse reactions to over-the-counter analgesics: an epidemiological evaluation", *Agents Actions Supplement*, Vol 25, 1988, pp21-31
64. Diamond, J., "They'll never swallow that", *Sunday Times Magazine*, 17 May 1987, pp82-4
65. BMA and the Royal Pharmaceutical Society of Great Britain, op cit, p18
66. Sandler, D.P. and Weinberg, C.R., "Analgesic use and chronic renal disease", *New England Journal of Medicine*, Vol 321, No 16, 19 Oct 1989, pp1126-7
67. Burk, R.F., "N-acetylcysteine in the treatment of acetaminophen overdose", *New England Journal of Medicine*, Vol 320, No 21, 25 May 1989, p1418
68. AMA, op cit, p75
69. Gilman, et al, op cit, pp665-6
70. *Physicians' Desk Reference*, Oradell, NJ, Medical Economics Company, 44th edn, 1990, p2293
71. Anon., "Junifen suspension – ibuprofen for febrile children", *Drug and Therapeutics Bulletin*, Vol 29, No 3, 4 Feb 1991, pp11-12
72. Reynolds, J.E.F. (ed.), *Martindale: The Extra Pharmacopoeia*, London, The Pharmaceutical Press, (29th edn) 1989, p1321
73. Anon., "Grünenthal pursues tramadol", *Scrip*, No 1509, 27 Apr 1990, p34
74. Offerhaus, L., "Glafenine: kiesplin of kiespijn?" (Glafenine: toothache or toothache?), *Nederlands Tijdschr Geneeskd*, Vol 132, No 40, 1988, pp1853-57
75. Anon., "Glafenine withdrawn in Belgium", *Scrip*, No 1581, 11 Jan 1991, p34. In 1991, glafenine was marketed in 78 countries, according to an article in *The Lancet* (Vol 339, 8 Feb 1992, p357).
76. Offerhaus, op cit, pp1853-57
77. Dukes, M.N.G. and Beeley, L. (eds), *Side Effects of Drugs Annual 12*, Amsterdam, Elsevier, 1988, p90
78. Offerhaus, op cit, pp1853-57
79. Stricker, B.H.Ch., de Groot, R.R.M. and Wilson, J.H.P., "Anaphylaxis to glafenine", *Lancet*, Vol 336, No 8720, 13 Oct 1990, pp943-4
80. Herxheimer, A., "Belgium: Withdrawal of glafenine", *Lancet*, Vol 337, No 8733, 12 January 1191, p102
81. BUKO Pharma-Kampagne, *Hoechst: A Cause of Illness?*, Bielefeld, BUKO Pharma-Kampagne, 1987, pp21-2
82. MaLAM letter to Roussel, June 1990
83. Anon., *Scrip*, No 1581, op cit, p34
84. Anon., 'Glafenine withdrawal recommended', *Scrip*, No 1685, 22 Jan 1992, p23
85. Anon., "Withdrawal of glafenine", *Lancet*, Vol 339, No 8789, 8 Feb 1992, p357
86. Anon., "Glafenine: voluntary withdrawal", *WHO Drug Information*, Vol 6, No 2, 1992, p57
87. Sanberg, P. and Krema, R.M.T., *Over-the-counter Drugs: harmless or hazardous?*, London, Burke Publishing, 1988, p49
88. Dubach, U.C., Rosner, B. and Stürmer, T., "An epidemiological study of abuse of analgesic drugs: effects of phenacetin and salicylate on mortality and cardiovascular morbidity (1968 to 1987)", *New England Journal of Medicine*, Vol 324, No 3, 17 Jan 1991, pp155-60
89. Sandler, D.P., Smith, J.C., et al, "Analgesic use and chronic renal disease", *New England Journal of Medicine*, Vol 320, No 19, 11 May 1989, pp1238-43
90. Stolley, P.D., "The risks of phenacetin use", *New England Journal of Medicine*, Vol 324, No 3, 17 Jan 1991, pp191-3
91. Graedon, J., *The People's Pharmacy - 2*, New York, Avon Books, 1980, p41
92. United Nations, op cit, p77
93. Ibid, pp76-8; Anon., "FRG voluntary phenacetin withdrawals", *Scrip*, No 1081, 3 Mar 1986, p3; Consumers' Association of Penang, *Drugs and the Third World: Phenacetin risks, benefits and marketing in Malaysia*, Penang, CAP, 1986, p4
94. Gilman, et al, op cit, pp654-5
95. Anon., "Hoechst in 1987 and 1988", *Scrip*, 23 Mar 1988, p14
96. Anon., "Good growth for Hoechst Pharma", *Scrip*, No 1702, 20 Mar 1992, pp8-9
97. Reynolds, op cit, p15
98. Laurence and Bennett, op cit, p168
99. Fuellgraff, G. and Palm, D. (eds), *Pharmakotherapie - Klinische Pharmakologie*, (6th edn), Stuttgart, Gustav Fischer Verlag, 1986, p194
100. AMA, *Drug Evaluations*, (2nd edn), Chicago, 1973, pp262-7
101. AMA, *Drug Evaluations*, (3rd edn), Chicago, 1977, p341
102. United Nations, op cit, p62
103. United Nations, op cit, p115
104. United Nations, op cit, pp62-3
105. United Nations, op cit, p89
106. United Nations, op cit, p90
107. Bennett and DeBroe, op cit, pp1269-71

Chetley, A. *Problem Drugs*, Amsterdam,
Health Action International, 1993

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4B. Dipyrone

A drug no one needs

Dr Kitima Yuthavong, the medical adviser of Hoechst's subsidiary in Thailand, said in 1987 that Baralgan – a product that contains dipyrone – "kills pain very effectively. Patients who are crawling with pain from intestinal colic will feel like a different person after taking the drug."[1]

In 1987, a young woman in Holland nearly died after being given Baralgin (Hoechst's brand name for a similar product in Europe) for vague abdominal complaints.[2] *Between July 1981 and July 1986, 94 people in Germany, where Hoechst is based, did die after taking products containing dipyrone. Agranulocytosis (severe loss of white blood cells, due to bone marrow damage) was the reason for 46 of the deaths, while 39 were due to anaphylactic shock, a severe allergic reaction.*[3]

Because of these deaths, in 1987 the German drug regulatory authority placed all dipyrone products on prescription and restricted their indications to severe pain after surgery or trauma, colic, or tumour pain. All combination drugs containing dipyrone were withdrawn, except for combination products containing a spasmolytic (like Baralgan/Baralgin), which were temporarily suspended pending resolution of an injunction taken out by another manufacturer.[4] Hoechst "voluntarily" withdrew Baralgin from the German market at the beginning of 1987.

Dipyrone is an analgesic (pain killer) with anti-inflammatory and antipyretic (fever-reducing) properties. It is the sodium sulphonate derivative of amidopyrine or aminopyrine and, like propyphenazone and phenylbutazone, it is a member of the pyrazolone group of chemicals. The drug was first introduced by the German manufacturer, Hoechst, in 1922. Dipyrone is known by many names: analgin, analginum, metamizol, aminopyrine-sulphonate sodium, sodium noramidopyrine methanesulphonate, sulpyrine, methampyrone, novamidazofen, natrium, novaminsulfonicum, noramidazophenum, and noraminophenazonum.

Bad health – good business

However, dipyrone continues to be a popular and profitable pain killer in many countries. In 1987, Hoechst's two dipyrone products – Novalgin and Baralgin – brought in more than US $190 million, just over 5% of its total world drug sales.[5] In 1991, Novalgin alone contributed 2.3% of the company's total sales and was Hoechst's sixth most popular drug with global sales of some $125 million.[6] In 1989, Novalgin and Baralgin, with sales of US $4.3

million, made up nearly 25% of Hoechst's total sales in Pakistan.[7] In 1990, Baralgan was India's sixth most sold branded drug on the public market (excluding sales to hospitals or government health centres), with sales reaching $5.2 million.[8] In the Philippines in 1990, Baralgin accounted for more than one-third of Hoechst's total sales.[9] In 1991 in Bolivia, Novalgina was the best-known and most commonly used analgesic. It was available without a prescription and was even being sold in the street markets.[10]

Many companies produce analgesics containing dipyrone or other pyrazolone derivatives. As Table 4B-1 indicates, nearly one in five of the analgesics on the market in 1990 in Africa, the Caribbean, the Middle East and Pakistan contained dipyrone or another pyrazolone derivative. In 1989, dipyrone was the most commonly used analgesic in Bulgaria.[11] In South Korea in 1989, 42 brands of dipyrone were produced by 33 companies.[12] In Yugoslavia in 1990, dipyrone was the drug with the second highest volume of use.[13]

The continued popularity of dipyrone and other pyrazolones is hard to justify in the face of the evidence of the risks of agranulocytosis and anaphylactic shock. A major textbook on clinical pharmacology notes that dipyrone is "notorious" in causing agranulocytosis and "need never be used, as there are adequate substitutes".[14] A German textbook on clinical pharmacology explains that the risk of dipyrone-induced shock is 1:50,000 users of the oral form, and could be 1:5,000 for injections.[15]

In 1980, the *Side Effects of Drugs Annual* concluded: "Since effective, less dangerous alternative drugs are available there is no case for the continued use of aminopyrine and dipyrone."[16] As long ago as 1973, the American Medical Association's *Drug Evaluations* said that the use of dipyrone "as a general analgesic, antiarthritic or routine antipyretic cannot be condoned."[17] In the 1977 edition, it was stated that the drug had become "obsolete in the US",[18] and any mention of it has disappeared from subsequent editions.

However many companies, Hoechst included, claim that dipyrone is a safe and effective product. According to Dr R. Timmers, head of Hoechst's division of Medical Affairs, dipyrone has an "outstanding safety margin" and "has proven itself since more than 60 years to be an effective and at the same time outstandingly well tolerated analgesic substance".[19]

The "Boston study"

In an effort to resolve the debate over the incidence of dipyrone-induced agranulocytosis, an International Agranulocytosis and Aplastic Anaemia

The other pyrazolones

Like dipyrone, the other pyrazolone derivatives tend to be associated with unpredictable allergic reactions or with life-threatening blood disorders.

amidopyrine: "The risk of agranulocytosis in patients taking amidopyrine is sufficiently great to render this drug unsuitable for use. Onset of agranulocytosis may be sudden and unpredictable."[1]

phenazone (antipyrine): "now used only as a marker of hepatic drug-metabolising activity"; even with this limited use, allergic reactions can occur.[2]

propyphenazone: anaphylactic shock has been reported with this drug.[3]

phenylbutazone: primarily used in the treatment of some types of arthritis (see the section on *NSAIDs* for more information); it is "poorly tolerated by a number of patients", and a number of deaths have occurred from aplastic anaemia and agranulocytosis.[4]

Sources:
1. Reynolds, J.E.F. (ed.), *Martindale: The Extra Pharmacopoeia*, London, The Pharmaceutical Press, (29th edn) 1989, p3
2. Dukes, M.N.G. and Beeley, L., (eds), *Side Effects of Drugs Annual 14*, Amsterdam, Elsevier, 1990, p92
3. Dukes, M.N.G. and Beeley, L., (eds), *Side Effects of Drugs Annual 12*, Amsterdam, Elsevier, 1988, p83
4. Gilman, A.G., Rall, T.W., Nies, A.S., and Taylor, P. (eds), *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, New York, Pergamon Press, (8th edn) 1990, p654

Table 4B-1
Number and percentage of analgesics containing a pyrazolone (1990)

Country/ Region	No. of analgesics	No. & % of drugs containing: dipyrone No.	%	other pyrazolones No.	%
Africa	115	18	16	9	8
Caribbean	66	12	18	6	9
Middle East	141	21	15	10	7
Pakistan	186	21	11	2	1
Total	508	72	14	27	5

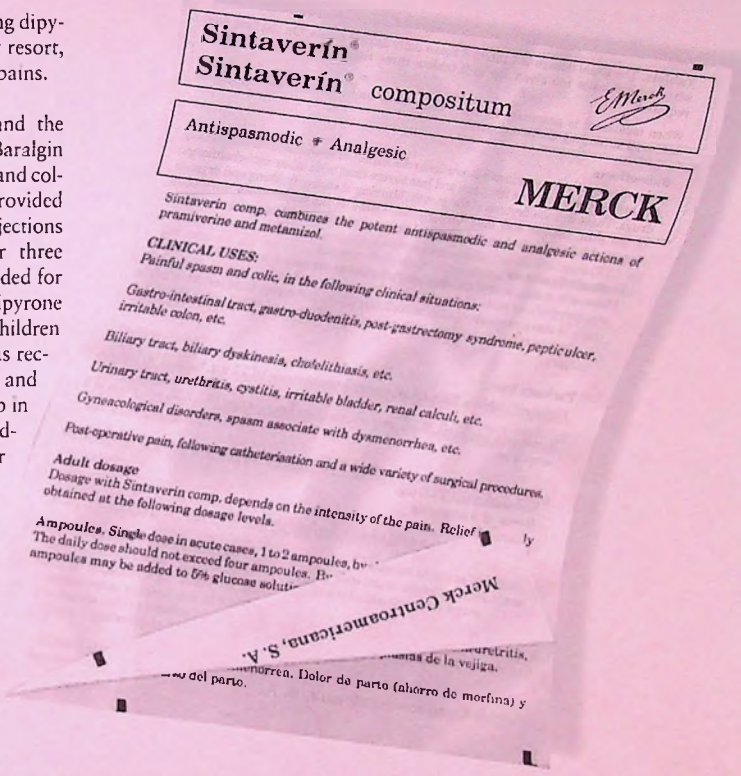
Sources: *Africa:* MIMS Africa *July 1990;* Caribbean: *MIMS Caribbean* July 1990; Middle East. MIMS Middle East Jun 1990; Pakistan: QIMP 1990

re-emphasised its view that mono-preparations of dipyrone were drugs of last resort, primarily for tumour pain.

Excessive promotion

In most parts of the world, products containing dipyrone are being promoted not as drugs of last resort, but for everything from headaches to period pains.

In Africa[30] and the Caribbean[31] in 1991 and the Middle East[32] in 1990, Hoechst's Baralgan/Baralgin was recommended for all types of "spasmodic and colicky pains" and conflicting information was provided about the use of the product in children. Injections were not recommended for children under three months of age and tablets were not recommended for children under six years of age, even though dipyrone was said to be generally contraindicated for children under 15 years of age. Hoechst's Novalgin was recommended for rheumatic pain, "headaches and toothache, after injuries and operations, cramp in the gastrointestinal region, the biliary tract, kidneys and lower urinary tract", and for "lowering high temperature" in diseases with fever. Medimpex's Ridol was promoted in the Middle East in 1990 for "pain and spasm" of the gastrointestinal or urinary tracts. In 1992, in Costa Rica, a package insert for E. Merck's Sintaverin (containing dipyrone and an antispasmodic, pramiverine) indicated the product for all types of "spasm and colic", including that caused by conditions such as "peptic ulcer", "cystitis" or "dysmenorrhoea" (menstrual pain).


Sintaverín®
Sintaverín® compositum
Antispasmodic + Analgesic
MERCK
Sintaverin comp. combines the potent antispasmodic and analgesic actions of pramiverine and metamizol.
CLINICAL USES:
Painful spasm and colic, in the following clinical situations:
Gastro-intestinal tract, gastro-duodenitis, post-gastrectomy syndrome, peptic ulcer, irritable colon, etc.
Biliary tract, biliary dyskinesia, cholelithiasis, etc.
Urinary tract, urethritis, cystitis, irritable bladder, renal calculi, etc.
Gyneacological disorders, spasm associate with dysmenorrhea, etc.
Post-operative pain, following catheterisation and a wide variety of surgical procedures.
Adult dosage
Dosage with Sintaverin comp. depends on the intensity of the pain. Relief
obtained at the following dosage levels.
Ampoules. Single dose in acute cases, 1 to 2 ampoules, by
The daily dose should not exceed four ampoules. By
ampoules may be added to 5% glucose soluti
Merck Centroamericana, S.A.
del parto.

Indications such as these were also reported in a 1986 survey[33] which looked at marketing claims from 1983 to 1985. Similar claims were also found in Asia, Africa and Latin America between 1987 and 1989.[34] With this irresponsible overpromotion, it is little wonder that products containing dipyrone have become such popular medicines in some countries, often available without prescription. Yet dipyrone has no advantage over less hazardous analgesics currently on the market. For simple pain, aspirin, paracetamol or ibuprofen are as effective. Codeine is useful for moderate pain. For severe pain, such as cancer pain or post-operative pain, standard advice is to use a strong opioid such as morphine, methadone or oxycodone.[35]

Contrary to Hoechst's claims, the Boston study failed to remove doubts about dipyrone's safety. If anything, it merely confirmed that here was a drug that no longer had a place in modern medicine.

The US Food and Drug Administration, which in 1977 withdrew approval of dipyrone because of its association with agranulocytosis and because of the availability of "alternative drug products and

Products containing propyphenazone

The other main pyrazolone derivative that is found today in pain killers is propyphenazone. Three Swiss companies – Ciba-Geigy, Sandoz and Hoffman-La Roche – are the principal manufacturers. Like dipyrone, propyphenazone products are usually promoted for a broad range of pains, as the table below indicates.

Company	Brand name	Indications (partial)
Ciba-Geigy[1]	Cibalgin	headache, dental pain, fever
Ciba-Geigy[1]	Spasmo-Cibalgin	painful spastic conditions, dysmenorrhoea
Roche[2]	Saridon(e)	pain, headache, toothache, menstrual pain, influenza, fever
Sandoz[2]	Optalidon	headache, toothache, dysmenorrhoea

Notes:
1. Africa and the Caribbean in 1991 and the Middle East in 1990
2. Africa in 1991 and the Middle East in 1990
Sources: Africa: *MIMS Africa*, July 1991; Caribbean: *MIMS Caribbean*, Jan 1991; Middle East: *MIMS Middle East*, June 1990

Study (IAAAS) was set up in 1978, partially funded by Hoechst, and carried out by the Boston University Drug Epidemiology Unit. This "Boston study" aimed to collect all reports of patients with agranulocytosis and aplastic anaemia that were admitted to hospital or occurred during a stay in hospital in eight locations: Israel, Barcelona, Ulm, West Berlin, Milan, Budapest, Sofia and Stockholm/Uppsala, with a total population of 22.3 million people. Attempts to collect data in Brazil and Indonesia were abandoned because it was not possible to ensure reliable data. Only five of those locations – Israel, Barcelona, Ulm, West Berlin and Budapest – were used for the calculations on dipyrone-induced agranulocytosis. The results[20] were surprising, and have triggered off even more debate.[21]

In three of the locations – Ulm, Berlin and Barcelona – the risk of agranulocytosis was 23.7 times higher from using dipyrone than from not taking the drug. However, in Israel and Budapest, the relative risk was less than one – a variation which the authors of the study were unable to explain. Nonetheless, they calculated an "excess risk" (or absolute risk) from dipyrone on the basis of the German and Spanish data of no more than 1.1 cases per million users per week. As *The Lancet* subsequently pointed out:

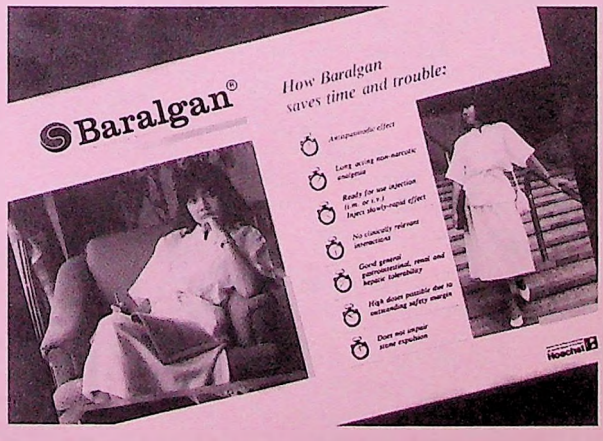
> "The calculation underlying this estimate is not explained. The peculiar denominator is difficult to apply to real life. The risk for exposure during one year could be up to 50 times higher. It would be expressed more clearly as the number of cases per million defined daily doses (DDD), or per 100,000 packs sold."[22]

No matter what the controversy over the risk attached to dipyrone, the study was useful in determining, without question, that dipyrone can induce agranulocytosis; that dipyrone was responsible for about one-quarter of the drug-induced cases of agranulocytosis in the participating countries; and that in some areas, patients who had taken dipyrone in the week before the study were 20-30 times more likely to develop agranulocytosis than those who did not use dipyrone.[23] The Boston study did not look at the other major adverse effect associated with dipyrone – anaphylactic shock.

Misleading interpretation

Hoechst declared that as the risk of dipyrone-induced agranulocytosis was proven to be "extremely low", the main "problem" with dipyrone for over 40 years was now "solved". Hoechst's marketing director, Dr Hans-Gunther Grigoleit, said "in view of the improved risk/benefit situation of dipyrone, there is no need to change the legal status of dipyrone towards more restrictions".[24] The *Side Effects of Drugs Annual* described this interpretation by Hoechst as "misleading", and pointed out that by taking into account the actual level of use of the drug, there could be over 7,000 cases of dipyrone-induced agranulocytosis each year.[25] Given that the fatality figures suggested by the IAAAS related to industrialised country settings, that previous estimates of agranulocytosis fatality rates in developing countries have ranged as high as 73%,[26] and that the major markets for dipyrone products now lie in developing countries due to restrictions on sales or outright bans in industrialised countries, it is reasonable to suggest that there could be at least 2000 deaths a year globally from dipyrone.[27]

The German drug regulatory authority – the BGA – also found Hoechst's interpretation of the Boston study difficult to accept. At a hearing held in September 1986, epidemiologists invited by the BGA challenged the statistical methods used in the study. The hearing also noted "the relative paucity of data on the basic pharmacology and pharmacokinetics of dipyrone, and the lack of knowledge about the immunological mechanisms underlying the adverse reactions and means of identifying vulnerable individuals. There were no adequate studies comparing its therapeutic efficacy with that of alternative drugs."[28] In addition to introducing the restrictions mentioned earlier, the BGA ruled that the use of dipyrone for other types of severe pain, such as toothache or migraine, or for high fever, was to be seen only as "a last resort when other analgesics are contraindicated".[29] In February 1990, the BGA issued an order banning all combination products containing dipyrone and



Hoechst advertises dipyrone's "outstanding safety margin" in Thailand in the late 1980s.

non-pharmacological therapies that would have less potential for risk", stated in 1988 that its position on dipyrone "has not changed".[36]

In 1987, William Jenkins, then a principal medical officer at the UK Department of Health, commented that "my personal views are the same as those expressed in *Martindale, The Extra Pharmacopoeia*, 28th edition.[37] Although arguments continue about the true incidence of serious and fatal adverse reactions to amidopyrine and dipyrone, I find the frequency unacceptable."[38]

In its editorial in 1986, *The Lancet* concluded that the findings of the Boston study "reinforce the arguments for banishing dipyrone and where possible using paracetamol or aspirin instead".[39]

Trying to preserve the market

Since 1986, Hoechst and many other companies have been trying to convince prescribers and drug regulatory authorities, particularly in developing countries, that dipyrone is a "safe" drug.

In Thailand, Hoechst's Manager, Phornvit Phacharintanakul, said that the company believed that Baralgan "scientifically and technically speaking, will pose no problem to users".[40] To reinforce the message, Dr R. Timmers, the head of the Hoechst's Medical Affairs division, visited Thailand several times and toured medical schools giving presentations on the Boston study. During his talks, he claimed that dipyrone was as "safe as aspirin". At the same time, Hoechst distributed copies of the Boston study, carefully highlighted to draw attention to its more favourable messages.[41]

Similarly, Dr Erhard Groll of E. Merck said the matter should be looked at on a country-by-country basis:

> "For instance, a drug which has passed clinical tests and was marketed in Germany was found to have caused a few fatalities after it was used among tens of thousands of consumers. As a result, it was withdrawn from the market. But if the same drug could save the lives of thousands of people in a developing country, then would it be morally wrong to export the drug to that country?"[42]

However, as the indications mentioned above demonstrate, dipyrone is not being promoted for life-threatening illnesses. People generally do not die from headaches or menstrual pains. This point is reinforced by the Medicines Commission of the German Medical Association:

> "Renal or biliary colic kills no one. For this reason, even a small risk of a life-threatening condition... is an unacceptable price to pay for pain relief, especially since it cannot be maintained that alternatives are not available".[43]

Dipyrone has been banned or severely restricted in Australia, Bangladesh, Canada, Denmark, Egypt, Fiji, Germany, Greece, Ireland, Israel, Italy, Japan, Malaysia, New Zealand, Norway, the Philippines, Saudi Arabia, Singapore, Sweden, the UK, the USA, and Venezuela, and combination products containing dipyrone have been banned in Pakistan.[44]

[See also the sections on *Analgesics* and *NSAIDs*].

Recommendation for action

It is time that dipyrone and the other pyrazolone derivatives were removed from the market worldwide. Dipyrone is not a safe drug. It is not an essential drug. It offers no significant therapeutic benefit for the risk it presents. Therefore, the only course of action is to ban dipyrone and other pyrazolone analgesics, immediately.

Notes and references:

1. Khanthong, T., "Hoechst asserts its drug not harmful", *The Nation*, 22 Oct 1987, p19
2. Zijlmans, J.M., Class, F.H.J. and Overbosch, D., "Baralgin, pijn of -penie?", *Ned Tijdschr Geneeskd*, Vol 131, 1987, pp500-1
3. BUKO Pharma Kampagne, *Hoechst, A Cause of Illness? The Pharmabusiness in the Third World*, Germany, May 1986, p19
4. Anon., "Federal Health Office decides on dipyrone", *Lancet*, 20-27 Dec 1986, pp1450-1; Anon., "BGA's metamizole comb suspension", *Scrip*, No 1208/9, 27-29 May 1987, p6
5. Anon., "Hoechst in 1987 and 1988", *Scrip*, No 1293, 23 Mar 1988, p14
6. Anon., "Good growth for Hoechst Pharma", *Scrip*, No 1702, 20 Mar 1992, pp8-9
7. Ahmad, S.R., *Bitter Facts About Drugs*, Karachi, HAI-Pakistan, 1990, p9
8. Anon., "Indian branded drug sales", *Scrip*, No 1650, 11 Sep 1991, p19
9. Anon., "German and Swiss companies' drug supplies to the Third World: how rational?", *Drug Monitor*, Vol V, No 11, Nov 1990, p141
10. Personal communication from O. Lanza, La Paz, 1 Sep 1992
11. Vlahov, V. and Bacracheva, N., "Agranulocytosis and dipyrone", *Lancet*, No 8673, 18 Nov 1989, p1215
12. Anon., "S Korean consumers highlight banned drugs", *Scrip*, No 1457, 20 Oct 1989, p23
13. Anon., "Top drugs in Yugoslavia", *Scrip*, No 1665, 1 Nov 1991, p22
14. Laurence, D.R. and Bennett, P.N., *Clinical Pharmacology*, (6th edn), Edinburgh, Churchill Livingstone, 1987, p168
15. Fuellgraff, G. and Palm, D. (eds), *Pharmakotherapie – Klinische Pharmakologie*, (6th edn), Stuttgart, Gustav Fischer Verlag, 1986, p194
16. Dukes, M.N.G., (ed.), *Side Effects of Drugs Annual 4*, Amsterdam, Elsevier, 1980, pp63-4
17. AMA, *Drug Evaluations*, (2nd edn), Chicago, 1973, pp262-7
18. AMA, *Drug Evaluations*, (3rd edn), Chicago, 1977, p341
19. Letter from Hoechst to the Medical Lobby for Appropriate Marketing, 21 Sept 1984
20. International Agranulocytosis and Aplastic Anemia Study, "Risks of agranulocytosis and aplastic anemia: a first report of their relation to drug use with special reference to analgesics", *Journal of the American Medical Association*, 256, 3 Oct 1986, pp1749-57
21. See for example:
    Faich, G.A., "Analgesic use and pharmacoepidemiology", *Journal of the American Medical Association*, Vol 256, No 13, 3 Oct 1986, p1788
    van Dijke, C.P.H., "Analgesic use, agranulocytosis, and aplastic anemia", *Journal of the American Medical Association*, Vol 257, No 19, 15 May 1987, p2590 (letter). Additional letters in the same issue and with the same heading were from: Feldman, U., et al; Kumana, C.; and a reply from Levy, M., et al.
    Anon., "Analgesics, agranulocytosis and aplastic anaemia: a major case-control study", *Lancet*, 18 Oct 1986, pp899-900
    Levy, M. and Shapiro, S., "Safety of dipyrone", *Lancet*, 1 Nov 1986, pp1033-4
    Dall, R., Lunde, P.K.M. and Maeschlin, S., "Analgesics, agranulocytosis and aplastic anaemia", *Lancet*, 10 Jan 1987, p101
    del Favero, A., "Analgesic use and risks of agranulocytosis and aplastic anemia", in: Dukes, M.N.G. (ed.), *Side Effects of Drugs Annual 11*, Amsterdam, Elsevier, 1987, pp89-91
    Offerhaus, L., "Metamizol: een honderdjarige treurnis" (Dipyrone: the sadness of a centenary), *Ned Tijdschr Geneeskd*, Vol 131, No 12, 1987, pp479-81
    Levy, M. and Shapiro, S., reply to Offerhaus, *Ned Tijdschr Geneeskd*, Vol 131, No 38, 1987, pp1680-1
    Offerhaus, L., rejoinder to Levy and Shapiro, *Ned Tijdschr Geneeskd*, Vol 131, No 38, 1987, pp1681-3
22. Anon., *Lancet*, 18 Oct 1986, op cit, pp899-900
23. del Favero, op cit, *p91*
24. *Anon., "Hoechst, dipyrone and agranulocytosis – the ISAAA study"*, Scrip, *No 1128, 13 Aug 1986, p22*
25. *Dukes*, 1987, op cit, p91
26. Henxheimer, A. and Yudkin, J.S., "Agranulocytosis and pyrazolone analgesics" (letter), *Lancet*, 31 Mar 1984, p730
27. Calculated by assuming at least 50% of consumption of dipyrone is in developing countries, and taking a 50% fatality rate results in some 1750 deaths, plus another 350 deaths in industrialised countries. If anything, that figure is liable to be an underestimate, given the difficulty (as the IAAAS itself demonstrated) of collecting reliable epidemiological data in developing country settings on the incidence of dipyrone-induced agranulocytosis.
28. Anon., "Dipyrone: Hearing by the German Drug Authority", *Lancet*, 27 Sep 1986, p737
29. Anon., "Federal Health Office decides on dipyrone", *Lancet*, 20/27 Dec 1986, p1450
30. *MIMS Africa*, Vol 31, No 4, July 1991
31. *MIMS Caribbean*, Vol 21, No 1, Jan 1991
32. *MIMS Middle East*, Vol 21, No 3, June 1990
33. Chetley, A. and Gilbert, D., *Problem Drugs*, The Hague/Penang, HAI, 1986
34. BUKO, *Dipyrone: a drug no one needs*, 1989, Bielefeld/Amsterdam, BUKO Pharma Campaign/HAI, pp11-12
35. Analgesic Guidelines Sub-Committee, Victorian Drug Usage Advisory Committee, *Analgesic Guidelines*, (1st edn), Toorak, Victorian Medical Postgraduate Foundation, 1988, pp32-3
36. Letter from Diane F. Walker, Consumer Safety Officer at the FDA to the Thai Drug Study Group, 21 March 1988, reproduced in: *Junkyard Thailand - Dumping of drugs and double standards in drug information: the case of dipyrone*, Bangkok, Drug Information for Action Centre, 1988, pp40-1
37. *Martindale* states, on page 251, that the use of dipyrone "is justified only in serious or life-threatening situations where no alternative antipyretic is available or suitable".
38. Silverman, M., Lydecker, M. and Lee, P.R., *Bad Medicine*, Stanford, Stanford University Press, 1992, p96, quoting a letter from Jenkins to the Chairperson of the Thai Study Group
39. Anon., *Lancet*, 18 Oct 1986, op cit
40. Khanthong, T., "Hoechst asserts its drug not harmful", *The Nation* (Thailand), 22 Oct 1987, p19
41. *Junkyard Thailand*, 1988, op cit; BUKO, *Pharma-Brief*, "Wie werden Medikamente in der Dritten Wel vermarktet? Zum Beispiel: Baralgan in Thailand", April 1988, pp2-3
42. Anon., "Germans prefer 'soft-sell' in patent protection issue", *Bangkok Post*, 3 Dec 1987
43. Rummel, W., "Metamizol: Kommentar zu Berichten über lebensbedrohliche Kreislauferkrankungen" (Dipyrone: commentary on reports of life-threatening circulatory disorders), *Deutschen Arztebiatt*, Vol 84(8), No 50, 10 Dec 1987, pp2408-11
44. United Nations, *Consolidated List of Products Whose Consumption and/or Sale Have Been Banned, Withdrawn, Severely Restricted or Not Approved by Governments*, 2nd issue, ST/ESA/192, New York, 1987, pp62-3; Anon., *Scrip*, No 1128, 1986, op cit; Anon., "Fiji bans import of certain products", *Scrip*, No 1529, 6 July 1990, p22; Balasubramaniam, op cit, p4; Anon., "Health ministry bans dipyrone combinations", *Lancet*, 17 Oct 1987, p905

Chetley, A. *Problem Drugs*, Amsterdam, Health Action International, 1993

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New sorts of aspirin in disguise – NSAIDs[1]

"NSAIDs are overvalued as symptomatic treatments, yet they continue to be prescribed in high quantities.... Empirical evidence suggests that a high proportion of long-term NSAID users can be safely switched to simple analgesics without compromising their therapy.... Not only would there be a real saving of health expenditure through the use of cheaper drugs, but also there would be a considerable reduction in mortality and morbidity from NSAID side-effects."[2]

Non-steroidal anti-inflammatory drugs (NSAIDs) are pain killers or analgesics. They work by blocking the production of chemicals called prostaglandins that are released at the site of any tissue damage. Prostaglandins stimulate nerve endings to pass the message to the brain that is interpreted as pain. They are also believed to be responsible for producing the inflammation that occurs at the site of tissue damage. So, NSAIDs can both block the sensation of pain and reduce inflammation. They are commonly prescribed for back pain, menstrual pain, headaches, mild pain following surgery, gout, and pain caused by strains or sprains. But their most common use is in the treatment of rheumatoid arthritis, osteoarthritis and other rheumatic conditions.[3]

Arthritis can be painful and crippling. Although there are many types, the two main categories are rheumatoid arthritis and osteoarthritis. Rheumatoid arthritis affects about 1% of the adult population worldwide.[4] Osteoarthritis is more common – about 15% of the world's population is affected.[5] In the USA, 80% of the population shows *some* evidence of osteoarthritis by the age of 65.[6] In the UK, at least 45% of people over the age of 65 have symptoms of arthritis. This leads to about one-third of all their consultations with a doctor.[7]

Types of NSAIDs

Salicylates
- aspirin
- diflunisal

Propionic acid derivatives
- benoxaprofen*
- fenbufen
- fenoprofen
- flurbiprofen
- ibuprofen
- ketoprofen
- nabumetone
- naproxen
- pirprofen
- tiaprofenic acid

Acetic acid derivatives
- diclofenac
- etodolac
- indomethacin
- sulindac
- tolmetin

Oxicams
- piroxicam
- tenoxicam

Butazones
- azapropazone
- oxyphenbutazone
- phenylbutazone

Sulphonanilides
- nimesulide

Other
- mefenamic acid

* withdrawn by the manufacturer for safety reasons

The symptoms of rheumatoid arthritis almost always include inflammation. In osteoarthritis, inflammation may not always be present or may be very mild. For this reason, osteoarthritis is sometimes also known as osteoarthrosis, to indicate disease rather than inflammation of the joint. In either condition, NSAIDs do not provide a cure.[8]

There are no well-designed controlled studies which show that NSAIDs are better than a simple analgesic such as paracetamol in the treatment of the symptoms of osteoarthritis.[9] While the efficacy of NSAIDs is not in doubt, their superiority over pure analgesics is "a matter of medical opinion" rather than being based on scientific evidence. Most studies of NSAIDs compare one with another or with a placebo. The few good studies that compare NSAIDs to analgesics have been able to show that NSAID treatment is only trivially superior or equivalent to pure analgesics for the relief of joint pain due to osteoarthritis.[10]

For most of this century, aspirin has been considered the drug of choice in the treatment of the symptoms of rheumatoid arthritis and similar conditions. Aspirin's major disadvantage is the need to give it regularly in fairly high doses to achieve sufficient anti-inflammatory action. At this dosage, aspirin produces adverse effects such as stomach upsets, gastric bleeding and noises in the ear. These may be reduced by taking aspirin after meals and/or by taking a buffered aspirin.[11]

Which drug to choose?

The adverse effects of aspirin are particularly a problem among the elderly – who are more likely to suffer from arthritis.[12] In an attempt to provide alternative treatment with fewer side effects, a new wave of drugs began to appear during the 1970s. There was soon a dazzling and confusing array of these NSAIDs on the market.

With so many drugs, it is difficult for physicians to know which is best. The World Health Organization's Essential Drugs List recommends acetylsalicylic acid (aspirin), ibuprofen, and indomethacin as the anti- inflammatory drugs to use. Ibuprofen and indomethacin are included as examples of a therapeutic group, and other drugs in the same group may be substituted depending on cost and availability.[13] In total, therefore, about 15 NSAIDs could be considered.

Five factors can help in the decision about which drug to use: efficacy, safety, individual response to the drug, convenience, and cost.

Cost

Most of the newer drugs on the market cost significantly more than the older, better known drugs. The use of an NSAID in the USA was found to be anywhere

Table 4C-1
Costs of NSAIDs in the UK in 1992

Generic name	Brand name	Maximum Daily dose	Cost/28 days (£)
Analgesics			
paracetamol	generic	4g	0.90
aspirin	generic	4g	1.64
ibuprofen	generic	2.4g	4.37
buffered aspirin	Palaprin	4g	5.60
NSAIDs			
phenylbutazone	Butacote	300mg	1.68
indomethacin	generic	200mg	3.08
aspirin	generic	8g	3.28
ibuprofen	generic	2.4g	7.62
ketoprofen	generic	200mg	8.09
ketoprofen	Orudis	200mg	8.09
piroxicam	generic	20mg	8.12
piroxicam	Feldene	20mg	8.87
indomethacin	Inocid	200mg	9.97
buffered aspirin	Palaprin	8g	11.20
sulindac	Clinoril	400mg	11.51
naproxen	generic	1.25g	11.55
mefenamic acid	generic	1.5g	11.59
mefenamic acid	Ponstan	1.5g	11.59
azapropazone	Rheumox	900mg	14.15
tiaprofenic acid	generic	600mg	15.13
diflunisal	generic	1.5g	15.16
diclofenac	Voltarol	150mg	15.32
diclofenac	generic	150mg	15.33
fluribprofen	Froben	300mg	15.46
nabumetone	Reliflex	1g	15.68
tiaprofenic acid	Surgam	600mg	15.89
tenoxicam	Mobiflex	20mg	16.52
etodolac	Lodine	600mg	17.14
naproxen	Naprosyn	1.25g	17.50
fenbufen	Lederfen	900mg	19.61
fenoprofen	Fenopron	3g	21.98
tolmetin	Tolectin	1.8g	44.72

Note: aspirin and ibuprofen are listed as both analgesics and NSAIDs as they are widely used as both simple pain killers (at lower dosages) and as anti-inflammatory drugs (at higher dosages).
Source: *British National Formulary*, No 23, Mar 1992

from twice to eight times the monthly cost of using a simple generic analgesic – like paracetamol or an analgesic dose of ibuprofen. If an NSAID was administered together with misoprostol to lessen the risk of NSAID-caused gastric ulcer, the costs were at least nine times that of simple analgesic therapy.[14] Table 4C-1 shows a similar comparison of products in the UK. Using a simple analgesic is much more cost effective; equally, NSAID strengths of aspirin or ibuprofen or the inexpensive NSAID, indomethacin, cost six to 14 times less than the most expensive NSAIDs.

Efficacy

Experts everywhere agree that "differences in efficacy have appeared relatively slight".[15] Reviews of 179 clinical trails of NSAIDs in osteoarthritis and more than 400 trials in rheumatoid arthritis have not demonstrated significant differences in efficacy, nor have they provided any basis to rank these drugs according to efficacy.[16] In another review of 196 trials that looked at NSAIDs in rheumatoid arthritis, more than 70 different effect variables were identified, making comparisons virtually impossible.[17] Although the number of NSAIDs has increased, none of the new NSAIDs have been proven to be more effective than aspirin.[18]

Safety

If the drugs have roughly equivalent efficacy, then their relative safety could provide a clue to appropriate selection. However, once again, with a few exceptions, there is little to choose. "There do not seem to be significant differences among these drugs – with the exception perhaps of ibuprofen at low doses – in the incidence of major side-effects."[19]

Tables 4C-2 and 4C-3 (on page 91) show two ways of looking at the relative safety of NSAIDs. Adverse reactions to NSAIDs among patients in Denmark over 15 years provided similar findings.[20] An attempt by researchers in the USA recently to develop a "toxicity index" of NSAIDs resulted in the identification of aspirin and ibuprofen as being among the least toxic, while indomethacin, tolmetin, meclofenamate and ketoprofen were the most toxic. However, the differences were only significant between the top three and bottom three drugs.[21]

As a class of drugs, "NSAIDs are one of the most common causes of adverse reactions reported to drug regulatory authorities".[22] In the UK, NSAIDs account for 5% of all drugs prescribed, but are responsible for 25% of all adverse drug reactions reported to the Committee on Safety of Medicines.[23] In the UK, an estimated 3,000 to 4,000 deaths each year are due to NSAID-related adverse effects.[24] In the USA, NSAID use leads to more than 70,000 hospitalisations and 7,000 deaths a year.[25] The toxic effects of NSAIDs often limit their usefulness in the elderly.[26]

Three major types of side effects are common with NSAIDs: gastrointestinal problems including gastric ulcer (see the box on the next page); kidney failure after long-term use; and cognitive dysfunction including forgetfulness, lack of concentration, sleeplessness, paranoia, and depression.[27] A less frequent side effect is liver damage, in some cases severe.[28]

Table 4C-2
Adverse reactions during the first five years of marketing in the UK

Drug	Serious adverse reactions (per million prescriptions)		
	Total	G/I	Deaths
indomethacin	n.a.	n.a.	3.3
ibuprofen	13.2	6.6	0.7
flurbiprofen	35.8	27.4	3.3
ketoprofen	38.6	33.2	1.6
diclofenac	39.4	20.9	3.1
naproxen	41.1	32.8	5.6
fenoprofen	43.7	32.3	6.6
diflunisal	47.2	33.5	3.5
sulindac	54.3	23.9	5.1
fenbufen	55.3	28.4	3.6
tolmetin	66.7	41.7	0.0
piroxicam	68.1	58.7	6.2
tiaprofenic acid*	80.0	75.0	10.0
azapropazone	87.9	67.0	9.9

*data based on less than 5 years marketing
Sources: *Scrip*, Nos 1102 and 1252, 14 May 1986 and 28 Oct 1987, p25 and p26; Cohen, P., "Non-steroidal anti-inflammatory drugs and serious gastrointestinal adverse reactions", *British Medical Journal*, Vol 293, 5 Jul 1986, p51

Individual response

An important variable with these products seems to be individual patient response. "Large variations are possible in the response of individuals to different aspirin-like drugs, even when they are closely allied members of the same chemical family."[29] Therefore, there needs to be a reasonable choice of products available, but it need not be large. A study in the Netherlands found that a small number of NSAIDs suffices to meet the needs of patients suffering from rheumatoid arthritis.[30] A small selection of drugs as advocated by WHO could easily be sufficient.

A profitable market

NSAIDs are good business. An obvious reason for concentrating on the development of NSAIDs is the size of the potential market for these products. NSAIDs are the most widely prescribed group of drugs worldwide.[31] Globally, more than 30 million

NSAIDs and ulcers

Gastrointestinal adverse effects are the most common problem with NSAIDs. NSAID users have about a three times greater relative risk than non-NSAID users of developing serious adverse gastrointestinal events. Patients over the age of 60 seem to be among those who are at the highest risk.[1] About seven out of every 10 NSAID users are subject to inflammation in the small intestine,[2] and about one out of every three NSAID users suffer from indigestion (dyspepsia).[3] However, the biggest problem is highlighted by an editorial in the journal, *Gastroenterology*: "Ulceration due to drugs is a major public health risk, because the use of aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) continues to increase. In part, this reflects overprescribing by physicians."[4] At any one time, between one in five and one in 10 NSAID users will suffer from an ulcer.[5] The cost of treating gastrointestinal complications caused by NSAIDs in the USA is estimated at $4 billion a year.[6]

Treatment of NSAID-related ulcers has opened up a new market area for the world's leading anti-ulcer drugs – H_2-blockers such as ranitidine and cimetidine and the new proton pump inhibitor, omeprazole. The traditional anti-ulcer drugs have been most successful in treating *duodenal* ulcers, which are less common than *gastric* ulcers.[6] There is some limited evidence to suggest that the prostaglandin analogue, misoprostol, may be effective in treating and preventing both gastric and duodenal ulcers.[7] However, misoprostol itself can cause adverse effects. Diarrhoea is reported in 25 to 40% of users, depending on dosage. Dr Sherine Gabriel of the Rheumatology Division of the Mayo Clinic notes that "diarrhoea is a dreaded event among disabled patients with arthritis with limited abilities for self care", which obviously impairs the quality of life of those affected.[8]

Misoprostol is produced by Searle, so it is not surprising that speakers at a Searle-sponsored press conference in the UK in October 1991 said that "misoprostol should be given to all NSAID patients at high risk of ulcer complications, particularly the elderly". It was estimated that this high-risk group would include about one-third of all NSAID users.[9]

Other commentators doubt the wisdom of this approach for dealing with NSAID-induced ulcers or "NSAID gastropathy" as it is increasingly being called. Dr J. Lacey Smith, a gastroenterologist in the USA, describes the term as a "cover-up". He says it should really be called "NSAID toxicity, or poisoning. The terminology is not academic, because the first principle of treatment for toxicities is removal or reduction of the offending agent, not the application of yet another drug on the poor poisoned patient, especially when we don't know if the proposed antidote works."[10]

Sources:
1. Gabriel, S.E., Jaakkimainen, L. and Bombardier, C., "Risk for serious gastrointestinal complications related to use of nonsteroidal anti-inflammatory drugs: a meta-analysis", *Annals of Internal Medicine*, Vol 115, No 10, 15 Nov 1991, pp787-96
2. Rooney, P.J. and Bjarnason, I., "NSAID gastropathy – not just a pain in the gut!", *Journal of Rheumatology*, Vol 18, No 6, 1991, pp796-7
3. Bush, T.M., Sholtzhauer, T.L., and Imai, K., "Nonsteroidal anti-inflammatory drugs: proposed guidelines for monitoring toxicity", *Western Journal of Medicine*, Vol 155, Jul 1991, pp39-42
4. Talley, N.J., "Chronic peptic ulceration and nonsteroidal anti-inflammatory drugs: more to be said about NSAIDs?", *Gastroenterology*, Vol 102, No 3, Mar 1992, pp1074-7
5. Nuki, G., "Pain control and the use of non-steroidal analgesic anti-inflammatory drugs", *British Medical Bulletin*, Vol 46, No 1, 1990, pp262-78
6. Day, R., and Henry, D., "Do anti-ulcer drugs prevent gastrointestinal damage from NSAIDs?", *Australian Prescriber*, Vol 14, No 3, 1991, pp42-3
7. Scheiman, J.M., "Pathogenesis of gastroduodenal injury due to nonsteroidal antiinflammatory drugs: implications for prevention and therapy", *Seminars in Arthritis and Rheumatism*, Vol 21, No 4, Feb 1992, pp201-10; Hayllar, J., Macpherson, A. and Bjarnason, I., "Gastroprotection and nonsteroidal anti-inflammatory drugs (NSAIDs): rationale and clinical implications", *Drug Safety*, Vol 7, No 2, 1992, pp86-105
8. Gabriel, S.E., "Is misoprostol prophylaxis indicated for NSAID-induced adverse gastrointestinal events? An epidemiologic opinion", *Journal of Rheumatology*, Vol 18, No 7, 1991, pp958-61
9. Anon., "Cytotec best in NSAI ulcer prophylaxis", *Scrip*, No 1664, 30 Oct 1991, p26
10. Lacey Smith, J., "What do you recommend for prophylaxis in an elderly woman with arthritis requiring NSAIDs for control?", *American Journal of Gastroenterology*, Vol 86, No 3, 1991, p266

people a day take an NSAID, and 40% are over the age of 60.[32] In Australia, more than 11 million prescriptions for NSAIDs are written each year,[33] accounting for 7% of all prescriptions.[34] In the UK, NSAIDs account for about 10% of the total annual pharmaceutical costs of the National Health Service,[35] and about 23 million NSAID prescriptions are dispensed each year.[36] In the USA, one in seven people is likely to be prescribed NSAID treatment each year;[37] while some 13 million of the country's 37 million arthritis patients take NSAIDs as therapy for chronic conditions.[38] NSAIDs account for more than 4% of the total prescription market in the USA – more than 100 million prescriptions are written each year for NSAIDs – and these figures do not include the aspirin and ibuprofen products available over the counter.[39] More than 40 billion aspirin tablets are used each year in the USA.[40]

The global market for products used in the treatment of arthritis was worth more than $6.7 billion in 1991, about 4% of the total world pharmaceutical

market. More than 90% of sales is for NSAIDs, making the global NSAID market worth over $6 billion. The largest market areas are Western Europe, with 27%, the USA with 24.5%, Japan with 19%, and Eastern Europe with 10%.[41] The US prescription market for NSAIDs is expected to reach $2.4 billion by 1995.[42] In 1989, NSAID prescription sales in the UK were more than £219 million ($395 million).[43]

Several individual products are major money-spinners for the companies producing them. Ciba-Geigy's diclofenac product, Voltaren, earned nearly $1.2 billion in 1991,[44] and Syntex's naproxen, Naprosyn, is predicted to reach the $1 billion mark in 1993;[45] its 1991 sales already exceeded $950 million. Pfizer's piroxicam, Feldene, is another strong product, with sales in 1991 reaching $680 million.[46]

Unnecessary risk

In a competitive rush to capture a share of this profitable market, some manufacturers have brought out many drugs in a blaze of advertising, only to have them quickly withdrawn when they were found to have a high incidence of serious side effects. One of the most infamous of these products was benoxaprofen, marketed by Eli Lilly as Oraflex or Opren. The box on the following page highlights the story of its withdrawal. The story of the butazones, a particularly hazardous group of NSAIDs is still unfolding. The box on page 93 explains the need for more action to be taken to remove the risk that these drugs pose. Some of the other drugs that have been withdrawn during the 1980s are listed in the box on page 94.

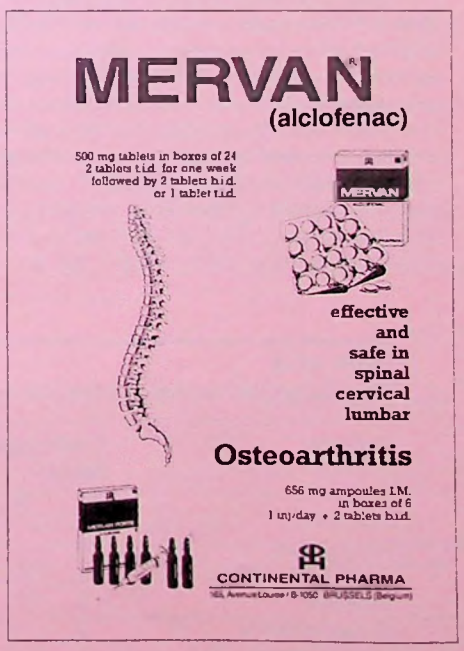
However, companies have sometimes been slow to withdraw these products in developing countries. Wyeth had its flufenamic acid derivative, Arlef, on the market in Africa in July 1991, although flufenamic acid products were taken off the market in the UK in 1984 because of safety concerns. Glenmark, an Indian company, had a paracetamol and oxyphenbutazone combination product, Flamox, on the market in the Middle East in December 1990, despite the banning of oxyphenbutazone in countries such as Norway and the UK by the end of 1984. Continental Pharma, a Belgian company, had a combination product, Neoston Forte, that included alclofenac on the market in Pakistan in 1990. Alclofenac was withdrawn in 1979 in the UK, Italy and New Zealand and in 1984 in Denmark. Pakistan ruled in 1987 that alclofenac should be deregistered for import. However, because there was no restriction on the sale of the drug, the product was allowed to remain on the market until "its stock [was] exhausted".[47]

In all, out of 460 NSAIDs on the market in developing countries during 1990 and 1991, 165 (36%) should be removed because of their poor safety

Table 4C-3
Comparison of NSAID-related deaths in the UK and the USA

Drug	Accumulated prescriptions* (x 1 million)		Estimated deaths per million prescriptions	
	UK	USA	UK	USA
Phenylbutazone	58.2	60.0	7.6	3.8
Indomethacin	57.8	51.3	4.9	2.2
Piroxicam	5.6	6.1	4.3	5.1
Sulindac	2.0	20.6	4.0	3.8
Naproxen	12.0	23.6	3.9	2.4
Diclofenac	3.2		1.9	
Ibuprofen	33.0	52.3	1.8	1.3

* Accumulated prescriptions since 1964 (UK), 1969 (USA), or introduction date
Source: Dukes, M.N.G. (ed.), *Side Effects of Drugs Annual 9*, Amsterdam, Elsevier, 1985, p87



Continental Pharma promoted alclofenac as "effective and safe" (MIMS Middle East, Dec 1988) in spite of prior withdrawals in the UK, Italy, New Zealand and Denmark.

records, their lack of significant therapeutic advantage over safer preparations, and, in most cases, their much higher cost (see Table 4C-4).

Promoting false claims

Because it is difficult to identify a scientific difference among the various NSAIDs, it is often left to the creative talents of marketing staff in the pharmaceutical industry to define a difference. Sometimes, however, that can lead to difficulties as Roussel, a subsidiary of Hoechst, found out to its cost. When Roussel launched its tiaprofenic acid derivative, Surgam, in the UK in April 1982, it used the slogan "potency with protection" and claimed the product relieved joint pain while being gentle on the stomach. There was no evidence for the claim, and the Department of Health took the unprecedented step of pressing criminal charges against the company and its medical director for misleading promotion that contravened the 1968 Medicines Act in the UK. In a court case that ended in 1987, the medical director was fined £1,000 and the company was fined £20,000 and had to pay a proportion of the prosecution costs.[48]

However, Roussel seems to be continuing its practice of stretching the claims for Surgam. One of the latest claims is that Surgam has "cartilage benefits" according to an advertisement in the December 1990 issue of *MIMS Middle East*, and that it "spares cartilage" according to advertisements in the March-August 1990 issue of *QIMP* in Pakistan. However, there is no clinical evidence to demonstrate that any NSAID has a beneficial effect on preventing cartilage damage or regenerating cartilage. Indeed, there has been a suggestion that NSAIDs may actually accelerate damage to cartilage.[49] In 1991, an editorial in *The Lancet* drew attention to Roussel's data sheet for Surgam in the UK which stated that laboratory experiments suggested "a neutral or possibly beneficial effect of tiaprofenic acid on joint cartilage". The data sheet added that "the clinical significance of these findings is not known but

Benoxaprofen

When it was launched in 1980, Opren (benoxaprofen) was described by Eli Lilly's Dr William Dawson as "the most significant advance in the treatment of arthritic conditions since aspirin", a claim that some rheumatologists agreed with. However, the aggressive promotion of the drug as being especially safe, and its subsequent overprescribing meant that far too many at-risk patients were exposed to the drug. In advertisements, the company claimed that "the side effects story as a whole is very impressive indeed, as they are generally mild and transient in nature".[1]
After just two years on the market, Opren was withdrawn worldwide by the company, because of the high incidence of side effects, including deaths. In the UK alone, at least 100 people are reported to have died and nearly 4,000 suffered side effects – mainly skin disorders and gastrointestinal disorders. More than 1,400 of the victims took Lilly to court for negligence.[2] At the end of 1987, Lilly offered the claimants a sum of £2.3 million (about £1,800 each) to settle the case out of court.[3] All but 28 of the victims accepted the settlement, even though it was 10 to 20 times less than the offer made to victims in the USA.[4]

Sources:
1. Opren Action Committee, *Briefing on Benoxaprofen (Opren)*, July 1985
2. Erlichman, J., "First offers to Opren victims", *Guardian*, 3 Jul 1987, p3
3. Lesser, F., "Drugs companies flinch at Opren settlement", *New Scientist*, 14 Jan 1988
4. Ferriman, A., "Drug victim Wilma's 'no' to handout", *Observer*, 14 Feb 1988

Table 4C-4
NSAIDs on the market in selected regions (1990-91)

Description	Country/Region Pakistan		Middle East		Africa		Caribbean		TOTAL	
	No.	%	No.	%	No.	%	No.	%	No.	%
No. of products	108		150		119		83		460	
On WHO Essential Drugs List	63	58.3	94	62.7	81	68.1	57	68.7	295	64.1
Butazones	17	15.7	7	4.7	4	3.4	6	7.2	34	7.4
Banned/withdrawn in another region	2	1.9	3	2.0	2	1.7	7	1.5		
Not recommended*	45	41.7	56	37.3	38	31.9	26	31.3	165	35.9

* Reasons for not recommending products are either a poor safety record, no therapeutic advantage over safer products, or higher cost.
Sources: *QIMP*, Mar-Aug 1990, Pakistan; *MIMS Middle East*, Dec 1990; *MIMS Africa*, Jul 1991; *MIMS Caribbean*, Jan 1991

Butazones: time to bury them

When phenylbutazone was launched in 1949, there were few other drugs on the market that could be used in the treatment of arthritis. Its main manufacturer, Ciba-Geigy, also introduced a related drug, oxyphenbutazone, in 1960. By the early 1980s, the two drugs together contributed more than 3.5% of Ciba-Geigy's global pharmaceutical turnover.[1]

Phenylbutazone and oxyphenbutazone have been described as "toxic and dangerous" with a long list of potential side effects.[2] Aside from the usual risks that can occur with any NSAID, the butazones are particularly likely to cause fatal blood disorders such as aplastic anaemia and agranulocytosis. Of the newer butazones, feprazone is chemically closely related to phenylbutazone, and has similar adverse effects. Azapropazone is less closely related and appears to be less toxic; blood disorders are less frequent, but rashes and gastrointestinal adverse effects are common.

In the early 1980s, a Ciba-Geigy memo revealed that phenylbutazone was responsible for at least 777 deaths between 1952 and 1981, and oxyphenbutazone was responsible for another 405 between 1960 and 1982.[3] Dr Sidney Wolfe of the US Public Citizen Health Research Group estimates that it is more likely to be over 10,000 worldwide, although the real total of deaths may never be known.[4]

The Ciba-Geigy memo was made public by Swedish paediatric neurologist, Dr Olle Hansson, who had received a copy of it from a source within the company. The public outcry led Ciba-Geigy to announce in April 1985 that by the end of September 1985, all its oxyphenbutazone products would be withdrawn worldwide and indications for Butazolidin (phenylbutazone) would be restricted to the "drug of second choice" in the treatment of: active ankylosing spondylitis; acute gouty arthritis; active rheumatoid arthritis; acute attacks of osteoarthritis.

In the UK, phenylbutazone is restricted even further: its only indication is as a second-line treatment of ankylosing spondylitis (arthritis of the spine) by hospital specialists.[5] Goodman and Gilman's text on pharmacology sums up the role of phenylbutazone succinctly: "at the present time, phenylbutazone is not considered to be the drug of choice for any condition".[6]

Other companies and other butazones

Although Ciba-Geigy has been the market leader, many other companies have butazone drugs on the market. As Table 4C-4 indicates, more than 7% of the drugs on the market in four regions of the world contain butazones. A survey carried out in 1987-8 found 21 oxyphenbutazone products for sale in Asia, Africa, the Middle East and Latin America.[7]

Aspirin and other NSAIDs are just as effective as phenylbutazone and much safer.[8] As clinical pharmacologist Andrew Herxheimer pointed out, the butazones have outlived their usefulness and "should be given a decent burial".[9] That means banning them all. Restrictions on indications are unlikely to work if the drugs are available in general practice or through pharmacies. Evidence from the USA shows that four years after Ciba-Geigy deleted the indication for osteoarthritis and thrombophlebitis for phenylbutazone, 392,000 prescriptions (17% of total) were issued for these indications. Dr. Sidney Wolfe told a hearing at the US Food and Drug Administration that: "Heavy promotion to treat inflammation of various kinds has locked many doctors into prescribing for this wide variety of indications.... The record shows that past labelling changes for these drugs has not deterred physicians from a large amount of prescribing for unapproved uses or for age groups or durations of therapy warned against in the label."[10]

Sources:
1. Hansson, O., *Inside Ciba-Geigy*, Penang, International Organization of Consumers Unions, 1989, p114
2. Chilnick, L.D. (ed.), *The Pill Book*, New York, Bantam Books, (4th edn) 1990, p699
3. Dukes, M.N.G. (ed.), *Side Effects of Drugs Annual 9*, Amsterdam, Elsevier, 1985, p87
4. Silverman, M., Lydecker, M. and Lee, P.R., *Bad Medicine: the prescription drug industry in the Third World*, Stanford, Stanford University Press, 1992, p16
5. BMA and the Royal Pharmaceutical Society of Great Britain, *British National Formulary*, London, BMA and The Pharmaceutical Press, No 23, Mar 1992, p349
6. Gilman, A.G., Rall, T.W., Nies, A.S., and Taylor, P. (eds). *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, New York, Pergamon Press, (8th edn) 1990, p655
7. Silverman, et al, op cit, p18
8. Wolfe, S.M., Fugate, L., et al, *Worst Pills Best Pills*, Washington, Public Citizen Health Research Group, 1988, p213
9. Silverman, et al, op cit, p18
10. Statement of Sidney M Wolfe, Director, Public Citizen's Health Research Group, before the US FDA Hearing on Petition for Imminent Hazard Ban of Phenylbutazone (Butazolidin) and Oxyphenbutazone (Tanderil), 31 Jan 1984, pp10-11

is being further investigated". *The Lancet* comments that "the wording is reasonable yet nevertheless seems designed to raise the possibility that this drug might be more than just another NSAID." The same comment about reasonableness cannot be made about Roussel's promotional claims in developing countries. The advice of *The Lancet* to its readers was that they "would be unwise to base their choice of NSAID on any supposed cartilage-sparing effect"[50] – advice that applies in every setting.

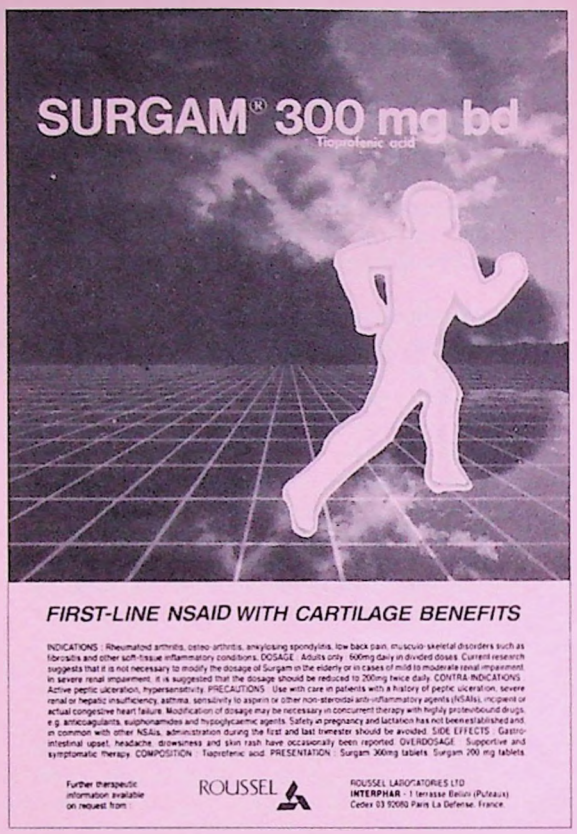
Time for action

As this section shows, the NSAID market is littered with dozens of very similar drugs. They may differ slightly chemically, but their therapeutic effects are almost indistinguishable. Their unwanted effects are also broadly similar. The past 20 years of research and development have not brought any significant breakthroughs in treatment, despite the appearance of a large number of drugs. If anything, the only result has been a more expensive way to inflict gastrointestinal upsets, ulcers, irritating skin rashes and other allergic conditions on patients already suffering from crippling pain. With the rush of new products there has also been an unnecessary lingering on the market of older products like the butazones whose hazards are beyond question.

Millions have been wasted. Thousands of people have died. Unnecessary suffering has been inflicted on an unknown number of people. It is time to introduce a more rational approach to the treatment of arthritis.

While analgesics are increasingly being recommended for use in arthritis instead of NSAIDs, many companies are trying to encourage the use of NSAIDs instead of analgesics in simple pain relief conditions. There is some reason for this, particularly if opioid or narcotic analgesics are being replaced, and if NSAIDs are used only for a short time. *The Lancet*, for example, suggests that post-operative pain relief may be a possible indication for NSAIDs.[51] Substituting NSAIDs for simple analgesics in the treatment of acute pain conditions such as headaches or menstrual pain, however, is not likely to be a wise or cost-effective decision. "These potent drugs with recognised dangerous side effects should be restricted in their prescription and used with caution for trivial and self-limiting complaints."[52] This is a particularly important point as more and more NSAIDs begin to come onto the market in many countries as over-the-counter drugs that do not require a prescription.[53]

In osteoarthritis, if a drug is needed, the first choice should be a simple analgesic like paracetamol. With rheumatoid arthritis, where NSAIDs may have some additional benefit, the first drug to use should be ibuprofen. If NSAIDs are used in osteoarthritis at all, they should be prescribed only in short courses to minimise the risk of serious adverse effects among



Roussel promotes Surgam's "cartilage benefits", MIMS Middle East, Aug 1990

NSAIDs that have been withdrawn in industrialised countries

alclofenac
benoxaprofen (Opren/Oraflex)
fenclofenac (Flenac)
feprazone (Methrazone)
flufenamic acid (Arlef)
indomethacin (controlled release preparations: Osmosin, Osmogit, Amuno Gits)
indoprofen (Flosint)
isoxicam (Maxicam)
oxyphenbutazone (Tandacote, Tanderil)
suprofen (Suprol)
suxibuzone
zomepirac (Zomax)

Questions to ask before prescribing/receiving an NSAID

Physician

1. Is the drug really required?
2. Should the dose be lowered?
3. Is the patient at risk from drug interactions and can the number of drugs be reduced?
4. Is this a high risk NSAID?
5. Is the patient a high risk patient and does he/she have another disease that puts him/her at risk?
6. Will the patient take the drug prescribed and what are the consequences if he/she does not do so?

Patient

1. Do I need this drug? Why? Is it for pain, inflammation or both?
2. Can I take a smaller dose? Is it safe to take a larger dose? How long do I need to take it?
3. Will this drug interact with other medicines I am taking? With food? Alcohol?
4. What are the adverse effects of this drug? Is there a safer drug available? Is there a non-drug therapy that would help?
5. Will this drug affect any existing illness that I have? Is there anything that I should be extra careful about?
6. What if I don't like the effects of this drug: can I stop taking it? What if I forget one or two tablets: will it affect the treatment?

Source: doctor's questions from: Nuki, G., "Pain control and the use of non-steroidal analgesic anti-inflammatory drugs", *British Medical Bulletin*, Vol 46, No 1, 1990, pp262-78

the elderly, as has been recommended by the National Drugs Advisory Board in Ireland,[54] and by the Australian Department of Health.[55]

An editorial in the journal *Gastroenterology* is clear that "until non-toxic alternatives are discovered, NSAIDs should be prescribed only when absolutely necessary, and then only in the lowest effective doses. Other agents (e.g., acetaminophen [paracetamol]) should be substituted where possible, particularly because NSAIDs in either analgesic or anti-inflammatory doses may not be superior to acetaminophen for the short-term symptomatic relief of osteoarthritis."[56]

Two doctors writing in the *New England Journal of Medicine* comment that manufacturers have an ethical responsibility "to exercise caution in marketing and to maintain surveillance" of NSAIDs since patients may well become daily users for long periods.[57]

The fashionable habit of prescribing an NSAID and misoprostol together as a means of minimising the most serious risk associated with NSAIDs (ulcers) is part of a worrying trend. The initial problem is caused by the administration of a drug; throwing a second drug at the problem – one which has its own troubling adverse effects – is clumsy at best and reinforces the "pill for every ill" mentality.

[See also the sections on *Analgesics* and *Dipyrone*.]

Recommendations for action

1. The marketing of any new NSAID should be restricted so that a carefully controlled number of patients receive the drug initially and so that its adverse reaction profile can be determined. As well, there should be an adequate independent system to monitor adverse drug reactions – sadly lacking in many countries. Therefore, governments and health authorities should take steps to establish such systems.

2. As equally effective and safer drugs are available, all butazones should be banned in all markets, immediately.

3. Regulatory bodies, health ministries and independent drug information units should urgently review the safety profiles of all NSAIDs on the market, with a view to limiting the number of preparations to the 10 with the best safety record, coupled with efficacy and low cost.

4. Products which have been withdrawn for safety reasons in one country should be withdrawn in *all* countries.

References:

1. Balme, H.W., "NSAIDs", (letter to the ed.), *Lancet*, 4 Feb 1984
2. Dieppe, P.A., Frankel, S.J. and Toth, B., "Is research into the treatment of osteoarthritis with non-steroidal anti-inflammatory drugs misdirected?", *Lancet*, Vol 341, 6 Feb 1993, pp353-4
3. Henry, J. (ed.), *The British Medical Association Guide to Medicines & Drugs*, London, Darling Kindersley, (2nd edn) 1991, pp77 and 112
4. Markenson, J.A., "Worldwide trends in the socioeconomic impact and long-term prognosis of rheumatoid arthritis", *Seminars in Arthritis and Rheumatism*, Vol 21, No 2 (Suppl. 1), Oct 1991, pp4-12
5. Ghosh, P. and Brooks, P., "Chondroprotection – exploring the concept", *Journal of Rheumatology*, Vol 18, No 2, 1991, pp161-6
6. Bradley, J.D., Brandt, K.D., et al, "Comparison of an antiinflammatory dose of ibuprofen, an analgesic dose of ibuprofen, and acetaminophen in the treatment of patients with osteoarthritis of the knee", *New England Journal of Medicine*, Vol 325, No 2, 11 Jul 1991, pp87-91
7. Nuki, G., "Pain control and the use of non-steroidal anti-inflammatory drugs", *British Medical Publication*, Vol 46, No 1, 1990, pp262-78
8. Parish, P., *Medicines: a guide for everybody*, London, Penguin (6th edn, revised), 1989, p197
9. Brandt, K.D., "The mechanism of action of nonsteroidal antiinflammatory drugs", *Journal of Rheumatology*, (Suppl. 27) Vol 18, 1991, pp120-1
10. Mazzuca, S.A., Brandt, K.D., et al, "The therapeutic approaches of community based primary care practitioners to osteoarthritis of the hip in an elderly patient", *Journal of Rheumatology*, Vol 18, No 10, 1991, pp1593-600
11. Parish, op cit, p197
12. Calkins, E., "Arthritis in the elderly", *Bulletin on the Rheumatic Diseases*, Vol 40, No 3, 1991, pp1-9
13. WHO, *The Use of Essential Drugs*, Fifth report of the WHO Expert Committee (Technical Report Series No 825), Geneva, WHO, 1992, p22
14. Mazzuca, et al, op cit
15. Fries, J.F., Williams, C.A. and Bloch, D.A., "The relative toxicity of nonsteroidal antiinflammatory drugs", *Arthritis and Rheumatism*, Vol 34, No 11, Nov 1991, pp1353-60
16. Champion, G.D., "Therapeutic usage of the non-steroidal anti-inflammatory drugs", *Medical Journal of Australia*, Vol 149, 15 Aug 1988, pp203-13
17. Gotzsche, P.C., "Sensitivity of effect variables in rheumatoid arthritis: a meta-analysis of 130 placebo controlled NSAID trials", *Journal of Clinical Epidemiology*, Vol 43, No 12, 1990, pp1313-18
18. Dumas, C. and Cusack, B.J., "Salicylate intoxication in the elderly: recognition and recommendations on how to prevent it", *Drugs & Aging*, Vol 2, No 1, 1992, pp20-34
19. Brooks, P.M., "Side-effects of non-steroidal anti-inflammatory drugs", *Medical Journal of Australia*, Vol 148, 7 Mar 1988, pp248-51
20. Anon., "15 years of NSAIs in Denmark", *Scrip*, No 1083, 10 Mar 1986, p4
21. Fries, et al, op cit
22. Brooks, P.M., "Clinical management of rheumatoid arthritis", *Lancet*, Vol 341, 30 Jan 1993, pp286-90
23. Anon., "Need for NSAI guidelines", *Scrip*, No 1741, 5 Aug 1992, p22
24. Hayllar, J., Macpherson, A. and Bjamason, I., "Gastroprotection and nonsteroidal anti-inflammatory drugs (NSAIDs): rationale and clinical implications", *Drug Safety*, Vol 7, No 2, 1992, pp86-105
25. Scheiman, J.M., "Pathogenesis of gastroduodenal injury due to nonsteroidal antiinflammatory drugs: implications for prevention and therapy", *Seminars in Arthritis and Rheumatism*, Vol 21, No 4, Feb 1992, pp201-10
26. Calkins, op cit
27. Ibid
28. Gay, G.R., "Another side effect of NSAIDs", *Journal of the American Medical Association*, Vol 264, No 20, 28 Nov 1990, pp2677-8
29. Gilman, A.G., Rall, T.W., Nies, A.S., and Taylor, P. (eds), *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, New York, Pergamon Press, (8th edn) 1990, p643
30. Wijnands, M., van Riel, P., et al, "Longterm treatment with nonsteroidal antiinflammatory drugs in rheumatoid arthritis: a prospective drug survival study", *Journal of Rheumatology*, Vol 18, No 2, 1991, pp184-7
31. Anon., "Misoprostol for co-prescription with NSAIDs", *Drug and Therapeutics Bulletin*, Vol 28, No 7, 2 Apr 1990, pp25-6
32. Zeidler, H., "Epidemiology of NSAID-induced gastropathy", *Clinical Rheumatology*, Vol 10, No 4, 1991, pp369-73
33. Day, R., and Henry, D., "Do anti-ulcer drugs prevent gastrointestinal damage from NSAIDs?", *Australian Prescriber*, Vol 14, No 3, 1991, pp42-3
34. Champion, op cit
35. Anon., "UK arthritis costs estimated", *Scrip*, No 1708, 10 Apr 1992, p5
36. Anon., "Misoprostol for co-prescription with NSAIDs", *Drug and Therapeutics Bulletin*, Vol 28, No 7, 2 Apr 1990, pp25-6
37. Brooks, 1988, op cit
38. Agrawal, N., "Risk factors for gastrointestinal ulcers caused by nonsteroidal anti-inflammatory drugs (NSAIDs)", *Journal of Family Practice*, Vol 32, No 6, 1991, pp619-24
39. Hoppmann, R.A., Peden, J.G., and Ober, S.K., "Central nervous system side effects of nonsteroidal anti-inflammatory drugs: aseptic meningitis, psychosis, and cognitive dysfunction", *Archives of Internal Medicine*, Vol 151, Jul 1991, pp1309-13
40. Jones, M.P. and Schubert, M.L., "What do you recommend for prophylaxis in an elderly woman with arthritis requiring NSAIDs for control?", *American Journal of Gastroenterology*, Vol 86, No 3, 1991, pp264-6
41. Anon., *The European Market for Arthritis Treatment Products*, London, Frost & Sullivan, 1991
42. Anon., *The US Market for Prescription Anti-inflammatory Agents*, New York, Frost & Sullivan, 1991, cited in: Anon., "US anti-inflammatory market $4 billion in 1995?", *Scrip*, No 1632, 10 Jul 1991, p18
43. Anon., *Scrip*, No 1708, op cit, p5
44. Anon., "Top 25 products in 1991", *Scrip*, No 1717, 13 May 1992, p28 (based on UBS Philips & Drew's *Global Pharmaceutical Review*)
45. Anon., "$270 million US sales for Ticlid?", *Scrip*, No 1586, 30 Jan 1991, p21
46. Anon., *Scrip*, No 1717, op cit, p28
47. Ahmad, S.R., *Bitter Facts About Drugs*, Karachi, HAI-Pakistan, 1990, pp233-4
48. Dyer, C., "The penalties of issuing misleading advertisements", *British Medical Journal*, Vol 294, 14 Feb 1987, pp426-7
49. Brandt, op cit; Rashad, S., Revell, P., et al, "Effect of non-steroidal anti-inflammatory drugs on the course of osteoarthritis", *Lancet*, No 8662, 2 Sep 1989, pp519-522
50. Anon., "Chondroprotection", *Lancet*, Vol 337, 30 Mar 1991, pp769-70
51. Anon., "Postoperative pain relief and non-opioid analgesics", *Lancet*, Vol 337, 2 Mar 1991, pp524-6
52. Gay, op cit
53. Bennett, W.M. and DeBroe, M.E., "Analgesic nephropathy – a preventable renal disease", *New England Journal of Medicine*, Vol 320, No 19, 11 May 1989, pp1269-71
54. Anon., "Nonsteroidal anti-inflammatory agents: hazards of long-term use", *WHO Drug Information*, Vol 5, No 1, 1991, p11
55. Anon., "NSAI restrictions on Australian PBS", *Scrip*, No 1790, 29 Jan 1993, p18
56. Talley, N.J., "Chronic peptic ulceration and nonsteroidal anti-inflammatory drugs: more to be said about NSAIDs?", *Gastroenterology*, Vol 102, No 3, Mar 1992, pp1074-7
57. Bennett and DeBroe, op cit

Chetley, A. *Problem Drugs*, Amsterdam,
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5A. Cough and cold preparations

Peddling placebos

Every year millions of people around the world come down with the "common cold". The symptoms are well known: a sore throat, a stuffy or runny nose, sneezes, perhaps a mild fever, some aches and pains and sometimes even an irritating cough.

The cause is also well known: one of more than 200 different strains from six families of viruses. From 30 to 50% of colds are caused by rhinoviruses, while coronaviruses account for some 15 to 20%. Respiratory syncytial, influenza, parainfluenza and adenoviruses cause most of the rest.[1]

Although the common cold is usually benign and self-limiting,[2] colds together with influenza and other acute respiratory infections (ARI) accounted for 48% of all short-duration (acute) illness in the USA in 1982.[3] More than three million people a year suffer from pneumonia in the USA, 500,000 of whom require hospitalisation.[4] Generally, in industrialised countries, acute respiratory diseases account for 25 to 50% of all medical consultations. About one-third of patients complain of common cold, one-third have symptoms of pharyngitis, laryngitis, or tonsillitis, and the remainder suffer from bronchitis, pneumonia or influenza.[5]

In China in 1989, respiratory diseases accounted for 25% of all deaths in rural areas.[6] In Africa, ARIs are the leading cause of illness and the main reason for the use of health services by children. ARIs account for an estimated 20 to 40% of children visiting outpatient clinics and as many as one-third of hospital admissions in Africa.[7] Globally, the World Health Organization (WHO) estimates that at least four million children under five years of age die each year from ARI-related infections – mostly pneumonia. That represents 10,000 deaths every day; two-thirds of those deaths occur in children under the age of one.[8]

Ineffective and a waste of money

There are no means to prevent or cure the common cold.[9] However, as long ago as 1933, H.S. Diehl wrote in the *Journal of the American Medical Association* that 35% of patients with colds who were treated with a lactose placebo reported good results. This finding led him to write: "it is possible to convince the public that practically any preparation is of value for the prevention or treatment of colds".[10] Over the years, the pharmaceutical industry has been very successful at doing precisely that, with the result that vast sums are spent every year trying to treat the untreatable.

A 1985 advertisement for cold remedies aimed at Australian pharmacists left no doubt about the company's intentions with its headline: "How to turn an

The use of antibiotics in the treatment of acute respiratory infections

Upper and lower respiratory tract infections are the primary cause of antibiotic use in general practice in patients of all ages.[1] A survey in pharmacies serving low-income populations in Fortaleza, Brazil found that antibiotics were routinely recommended for acute respiratory infections.[2] However, 95% of all acute infections of the upper respiratory tract are caused by non-bacterial organisms.[3] According to the American Medical Association (AMA), "routine administration of antimicrobial agents to patients with colds has been shown to be completely useless".[4] Only if the symptoms fail to abate within one to two weeks is there some possibility that a secondary bacterial infection of the sinuses, the ears, bronchial tract or lungs may be present. In the meantime, appropriate diagnostic studies could be carried out to determine whether treatment with penicillin, ampicillin, amoxycillin, co-trimoxazole or erythromycin may be needed.

Inappropriate antibiotic treatment of ARI in developing countries wastes the resources of health services and can increase the occurrence of drug-resistant bacteria.[5] WHO says that in most ARI cases, "antibiotics are not necessary".[6] In children less than five years old with a cough or difficult breathing, fast breathing or chest indrawing will identify the children who need antibiotic treatment for pneumonia. Fast breathing is defined as a respiratory rate of more than 60/min for infants under two months, 50/min for two months to one year, and 40/min for one year to five years. Children who have chest indrawing, or who have other danger signs of severe disease (not able to drink, abnormally sleepy or difficult to wake, convulsions, a calm child who makes a harsh noise while inhaling [stridor], or severe malnutrition) should be referred to hospital for treatment. If children have a cough without these signs, signs of an acute ear infection or of suspected streptococcal throat infection, they have a simple cough or cold and can be cared for at home *without* antibiotics or any commercial drugs.[7] For example, in Indonesia children with mild ARI were treated with either ampicillin or a placebo. Researchers found that the children who were given ampicillin did not improve any faster.[5]

Four simple rules have been developed to deal with children who have a cough:[8]

1. Most children with a cough do *not* need an antibiotic;
2. If there is coughing and fast breathing, oral co-trimoxazole or amoxycillin, or intramuscular injections of procaine penicillin are recommended;
3. If there is coughing and chest indrawing, the child should be referred to hospital and given intramuscular benzylpenicillin (with gentamicin if the child is under two months of age);
4. If there is coughing and cyanosis (bluish discoloration of the skin due to lack of oxygen in the blood) or the child cannot drink, the child should be admitted to hospital and given intramuscular injections of chloramphenicol (or benzylpenicillin with gentamicin if the child is under two months of age).

A study in Nepal found that even if referral facilities were lacking, village health workers and semi-literate parents could be trained to recognise and treat pneumonia with two oral antibiotics: first, cotrimoxazole and, if there was no improvement, oral chloramphenicol. After three years, there was a 30% reduction in death rates due to pneumonia.[9] An analysis of nine studies (including the one in Nepal) found a reduction in infant mortality from pneumonia of between 26 and 35%.[10]

According to WHO, improved understanding about the correct use of antibiotics in the treatment of bacterial pneumonia has led to the prevention of children's deaths. In some countries, this has also led to a reduction in the misuse of antibiotics for other forms of ARI.[11]

Sources:

1. Bergogne-Berezin, E.; "Continuous activity of significant antibiotics", *Clinical Therapeutics*, Vol 13, No 1, 1991, pp181-8
2. Misago, C. and Fonseca, W., "Antimicrobial drugs advised in pharmacies in Brazil for children with acute respiratory infections", *Lancet*, Vol 338, No 8768, 14 Sep 1991, p702
3. Lode, H., "Respiratory tract infections: when is antibiotic therapy indicated?", *Clinical Therapeutics*, Vol 13, No 1, Jan-Feb 1991, pp149-156
4. AMA, *Drug Evaluations*, Philadelphia, W.B. Saunders Co., (6th edn) 1986, p376
5. Sutrisna, B., Frerichs, R.R. and Reingold, A.L., "Randomised, controlled trial of effectiveness of ampicillin in mild acute respiratory infections in Indonesian children", *Lancet*, Vol 338, No 8765, 24 Aug 1991, pp471-4
6. Chetley, A., *Peddling Placebos. An analysis of cough and cold remedies*, Amsterdam, HAI, 1990, p1
7. WHO, *Acute respiratory infections in children: Case management in small hospitals in developing countries. A manual for doctors and other senior health workers*, (WHO/ARI/90.5), Geneva, WHO, 1990
8. Anon., *Childhood Pneumonia: strategies to meet the challenge*, (Proceedings of the First International Consultation on the Control of Acute Respiratory Infections, 1991). London, AHRTAG, 1992
9. Pandey, M.R., Daulaire, N.M.P., et al, "Reduction in total under-five mortality in western Nepal through community-based antimicrobial treatment of pneumonia", *Lancet*, Vol 338, 19 Oct 1991, pp993-7
10. Sazawal, S., and Black, R.E., "Meta-analysis of intervention trials on case-management of pneumonia in community settings", *Lancet*, Vol 340, 29 Aug 1992, pp528-33
11. Gove, S., Pio, A., et al, "WHO guidelines on detecting pneumonia in children", *Lancet*, Vol 338, 7 Dec 1991, p1453; Anon., "Towards a more rational use of antibiotics in acute respiratory infections in children", *Essential Drugs Monitor*, No 9, 1990, p5

unhealthy customer into a healthy profit". The rest of the text continued: "There's nothing like a cold winter to blow a hot profit your way. Especially when you've stocked up on these proven money spinners from Robins."[11] The conflicting and often ridiculous claims made in promotional material for cough medicines are described in the box on page 103.

In 1990, the world market for over-the-counter (OTC) cough and cold remedies was at least $7.3 billion. By the year 2000, analysts estimate the figure could be more than $9.5 billion.[12] The US market for cough and cold preparations was worth $5.5 billion in 1988 (35% of which was for prescription-only products) and is expected to reach sales of $7.8 billion (40% on prescription) by 1993, according to market analysts Frost and Sullivan.[13] In the Philippines in just six months in 1987, people in the capital city of Manila spent an estimated $3.1 million on cough syrups.[14] In the UK, cough and cold remedies account for 25% of the market for OTC drugs;[15] in 1991, an estimated £152 million (US$ 275 million) was spent on OTC cough and cold products.[16] In Germany in 1991, DM 875 million ($547 million) was spent on self-medication with cough and cold products.[17]

Paying through the nose

One of the most ineffective ingredients in cold remedies is an antihistamine, usually included in the mistaken belief that it will help to dry up a runny nose, and therefore make it easier to breathe. Although antihistamines are effective in dealing with rhinitis (inflammation of the nose) caused by allergic reactions, numerous studies of antihistamines (including the newer so-called non-sedating antihistamines) in the treatment of the common cold have yielded inconclusive results.[18] Dr Leslie Hendeles, professor of pharmacy and paediatrics at the University of Florida, points out that "since antihistamines have the potential to cause harmful effects, the risks associated with their use outweigh any meagre benefit. It is my opinion that these drugs should be removed from all non-prescription products promoted for the relief of cough and cold symptoms."[19]

Most authoritative texts agree that there is "no evidence" that antihistamines "are of the slightest value" in the treatment of rhinitis resulting from colds.[20] One pharmacology textbook points out that although they may have a weak effect on runny noses, "this drying effect may do more harm than good" and their sedative effect may also be harmful.[21] There is also evidence to suggest that the new non-sedating antihistamines can cause fluctuations in heart rhythms, some of which have been fatal.[22]

If antihistamines were used rationally, that is, used for the treatment of allergic rhinitis, it would be expected that most sales would occur during peak hay fever seasons. In a country such as the UK, this would most likely be during June to September. However, a year-long study of antihistamine prescribing in four socio-economic areas in Liverpool in the UK found antihistamine use was at its highest in January and at its lowest from June to September.[23] With the large number of cough and cold products which contain antihistamines, it is probable that similar patterns occur in other countries.

Nasal decongestants – usually sympathomimetics (drugs which mimic the stimulation of the sympathetic nervous system) – are also popular ingredients in cough and cold remedies. However, most nasal decongestants can cause problems. Decongestant nasal sprays, drops or inhalers may work for a short time. However, they are liable to lead to a "rebound effect" in that after they have been used, the congestion returns even more strongly. They may prolong a cold and repeated use may damage the lining of the nose.[24] The British Medical Association (BMA) says that "most common colds do not need to be treated with decongestants".[25] If a decongestant is needed, sprays, drops or inhalers containing oxymetazoline or xylometazoline could be used for a day or two; however, a simple salt and water solution (0.9%

Antihistamines used in cough and cold remedies

azatadine
bamipine lactate
brompheniramine
chlorpheniramine
clemastine
clemizole
cinnarizine
carbinoxamine
doxylamine
diphenhydramine
diphenylpyraline
isothipendyl
mebhydrolin napadisylate
mepyramine
oxomemazine
phenindamine
pheniramine
pimithixine
promethazine
phenyltoloxamine
terfenadine
thenyldiamine
tripelennamine
triprolidine
trimeprazine

saline) is "effective, cheap and may be useful in young children".[26]

Many cold preparations now contain nasal decongestants in tablet or syrup form, as this is thought to make the drugs more convenient to take. However there is little evidence that they are effective. The *British National Formulary* (BNF) says oral nasal decongestants "are of doubtful value".[27] Moreover, "nasal decongestants taken by mouth... produce constriction of other blood vessels in the body and increase the blood pressure.... They are best avoided."[28] They may also cause adverse behavioural changes in young children. Two doctors in the USA who reported two cases of such behavioural change in 1987 said their experience caused them "to question the routine use of over-the-counter decongestants in the treatment of children with upper respiratory infections".[29]

Hard to swallow

For many people, a sore throat is the first indication that a cold has started. This irritation of the throat is caused by the viral infection. There is "no convincing evidence" that antiseptic lozenges and sprays or commercial gargles are of any benefit.[30] Many sprays and lozenges contain a local anaesthetic, which may relieve pain, but can irritate the throat; making the pain worse when the anaesthic wears off. Nearly two million bottles of one throat spray, Chloraseptic, were sold in 1989 in the UK. However, it also was linked to swelling of the throat and larynx that could cause respiratory difficulties (including one death), and its use in children under six was contraindicated in 1990.[31]

Some "cough" lozenges contain soothing substances such as honey, liquorice or glycerin which may act on the surface of the throat. They may also contain pleasant smelling and tasting substances such as peppermint, eucalyptus, cinnamon, lemon, clove or aniseed. "The main effect of these preparations is that their smell or taste may help you feel better. They may increase the production of saliva, which is soothing and helps to wash the inflamed surfaces of the throat.... Cough medicines which contain the same ingredients in liquid form are even more irrational since they are swallowed directly into the stomach and only have a fraction of a second to work locally on the throat."[32]

Coughs – medicines or myths?

Cough is the single most common reason for patients to visit a doctor in Australia, accounting for more than 10% of all visits.[33] A cough is generally a useful reflex which serves to get rid of inhaled foreign bodies or to clear the air passages of sputum.[34] Such a cough is described as "productive". A cough which is simply dry and irritating serves no purpose and is called "unproductive." In most cases of acute cough no medicine is needed, unless there is evidence of more serious lower respiratory illness.[35]

However, a whole mythology has developed around various types of cough remedies. There are basically two types of drugs: expectorants or mucolytics, which supposedly help to expel the sputum more easily – and suppressants – which supposedly work to stop the coughing reflex.

Most expectorants act by irritating the lining of the stomach which in turn causes a reflex stimulation of

Oral nasal decongestants

The most commonly used oral nasal decongestants are ephedrine, phenylephrine, phenylpropanolamine and pseudoephedrine. Like all sympathomimetics, they should be avoided by people with hypertension, hyperthyroidism, coronary heart disease, or diabetes, and by people taking monoamine-oxidase inhibitors (used as antidepressants).[1]

Ephedrine
Because of its stimulant effect, ephedrine should not usually be given after 4pm. It is contraindicated in women who are breastfeeding, its safety in pregnancy has not been established, and it is not usually prescribed to people over 60 years of age.[2,3]

Phenylephrine
Phenylephrine is not usually prescribed in pregnancy as it may cause heart defects in the unborn baby, it is not usually recommended for infants, and adverse effects are more likely in people over 60.[3]

Phenylpropanolamine
Phenylpropanolamine is not recommended for children under eight, its safety in pregnancy has not been established, adverse effects are more likely in people over 60, and it has been associated with serious toxicity.[3,4,5]

Pseudoephedrine
Pseudoephedrine has been associated with rare incidences of visual hallucinations in children.[2]

Sources:
1. BMA and the Royal Pharmaceutical Society of Great Britain, *British National Formulary*, London, BMA and the Pharmaceutical Press, No 23, Mar 1992 p130
2. Reynolds, J.E.F. (ed.), *Martindale: The Extra Pharmacopoeia*, London, The Pharmaceutical Press, (29th edn) 1989, pp1462 and 1478
3. Henry, J. (ed.), *The British Medical Association Guide to Medicines & Drugs*, London, Dorling Kindersley, (2nd edn) 1991, pp265, 340 and 341
4. Lowenstein, S.R. & Parrino, T.A., "Management of the Common Cold", *Advances in Internal Medicine*, 32, 1987, p219
5. Orson, J. & Bassow, L., "Over the Counter Cough Formulas", *Clinical Pediatrics*, June 1987, p287

the nerves supplying the glands in the bronchi. This is said to result in an increased production of secretions, thus making the sputum more watery and easier to cough up. However, most of these drugs produce nausea and even vomiting at doses high enough to increase the secretions.[36] According to the BNF "there is no evidence that any drug can specifically facilitate expectoration".[37] For this reason, expectorant cough medicines have been described as "an expensive myth".[38] There is no rationale for their use.[39]

Mucolytics – such as acetylcysteine, carbocistene and methylcysteine – and other enzymes have been shown to "digest" sputum in the laboratory but their effect in real life situations has been variable. "Few patients... have been shown to derive much benefit from them."[40]

Most experts agree that there are few occasions when a cough suppressant should be used. According to the BNF:

> "The drawbacks of prescribing cough suppressants are rarely outweighed by the benefits of treatment and only occasionally are they useful, as for example, if sleep is disturbed by a dry cough. Cough suppressants may cause sputum retention and this may be harmful in patients with chronic bronchitis and bronchiectasis. Though commonly used in acute bronchitis and pneumonia, they can be harmful; such conditions are best treated by prompt administration of antibacterial drugs. Cough suppressants such as codeine, dextromethorphan, and pholcodine are seldom sufficiently potent to be effective and all tend to cause constipation. The use of cough suppressants containing codeine or similar opioid analgesics is not generally recommended in children and should be avoided altogether in those under 1 year of age."[41]

A Finnish study in 1991 found that the most common cause of cough is acute viral respiratory infection. This type of cough is usually transient and self-limiting and does not need treatment. The study concluded that cough suppressants should not be routinely used in the treatment of children with acute viral infection.[42]

According to the AMA, "reports on the effectiveness of various antitussive agents [cough suppressants] frequently conflict because of the difficulties in assessing their effects". One that does work, providing it is given at the appropriate dosage level, is codeine – although it can cause constipation and may, very rarely, produce drug dependence of the morphine type in some patients. The AMA describes it as "the most efficacious antitussive in the treatment of acute and chronic cough caused by a wide variety of disease states",[43] and it is the only cough medicine suggested in the WHO Essential Drugs list.[44]

The WHO list does indicate, however, that codeine should be considered as an example of a therapeutic group and that a similar drug such as dextromethorphan could be used. The AMA describes dextromethorphan as "the safest antitussive available" and as being "as effective as codeine except for severe acute cough".[45]

Combined mayhem

One of the most irrational types of products on the market is a combination of ingredients which are supposed to act as expectorants or mucolytics with those which act to suppress coughs. The vast majority of products sold as cough and cold remedies are combination products. The BNF says:[46]

> "Compound cough preparations have no place in the treatment of respiratory disorders.... Such preparations are to be *deprecated* not only as irrational but also for leading to patients receiving inappropriate drugs."

The US Food and Drug Administration (FDA) has concluded that "no significant target population exists which could benefit from a combination product containing more than three pharmacologic groups".[47] Similarly, the AMA says that if a combination is to be used, it should meet the following criteria:

1. It contains no more than three active ingredients from different pharmacologic groups and no more than one active ingredient from each pharmacologic group.
2. Each active ingredient is present in an effective and safe concentration and contributes to the treatment for which the product is used.
3. The product is used only when multiple symptoms are present concurrently.

Ingredients used as "expectorants"

acetates
acetic acid
ammonium chloride
benzoin compounds
bicarbonates
creosote
eucalyptus
guaiphenesin (glyceryl guiacolate)
ipecacuanha
menthol
peppermint
potassium iodide
sodium benzoate
sodium citrate
squill
tolu

4. The product is therapeutically appropriate for the type and severity of symptoms being treated.
5. The possible adverse reactions of the components are taken into consideration.

The AMA then comments: "many mixtures popular with the lay public and physicians for treatment of upper respiratory tract disorders do not meet these criteria".[48]

The AMA's comment is, if anything, an understatement. A survey of prescribing guides from 12 regions of the world during late 1987 and 1988, found that well over one-third of the 2,198 cough and cold preparations listed contained more than three ingredients. A staggering 86% of all the products listed contained ingredients deemed by independent sources to be ineffective in the treatment of cough and colds. And, to add injury to insult, 55% of the products contained ingredients liable to cause harmful adverse reactions.[49] The situation is not improving. A survey of prescribing guides in four regions during 1990 and 1991 found similar results, as Table 5A-1 on the next page shows.

To put the scale of the problem into a little more perspective, in most cases, the products listed in commercial prescribing guides represent only a small proportion of drugs likely to be on sale in any country. As a researcher in India pointed out, the *Monthly Index of Medical Specialities* listed only some 6% of the estimated 30,000 brands of all drugs on the Indian market. He commented: "the most obnoxious and downright criminal drugs are largely, though not entirely, eliminated" from the lists in the prescribing guide.[50]

Also, these surveys do not analyse products on the market in industrialised countries. The market in developing countries is a more obvious indicator of irrational therapies; however, the problem is not limited to them. In the UK in 1992, the *British National Formulary* listed 60 preparations for coughs or for nasal decongestion. It described 50 of them (83%) as "less suitable for prescribing".[51] A guide to over-the-counter medicines in France published in 1992, said that of the 276 cough medicines, "only a dozen are worthy of a place in the medicine cabinet".[52] Even that may be an overgenerous statement.

An editorial in *ARI News* sums up the situation succinctly:[53]

> "While millions of children die each year for lack of lifesaving therapy for severe ARI, many more are overtreated with unnecessary, potentially harmful drugs for mild ARI. Mild ARI nearly always gets better without the need for drug treatment.... A huge range of substances are now produced and promoted as the answer to the problems of ARI.... Not only may they give parents a false sense of security about a sick child, they may also be an expense families cannot afford, using up family income that could be better spent.

The glut of ineffective medicines on the market interferes with appropriate therapy. An international conference on ARI held in 1991 made the point that "enormous government and individual expenditure is committed to ineffective and potentially harmful treatments, while antibiotics vital for pneumonia treatment are unavailable".[54] On the other hand, this conference stressed that a solution is possible: "If parents can be persuaded by inaccurate messages about ineffective medicines, then it should also be possible to reach them with accurate information and low-cost treatments which will genuinely protect their children's lives."[55]

Treating coughs and colds

Most people with a cold need no drugs at all. The illness will run its course in anything from four to 14 days. Plenty of rest and warm fluids in the early stages of the infection are helpful. Paracetamol, used sparingly, can ease aches, pain and fever (although the usually mild fever is part of the body's defence mechanism against the infection).

When the nose is blocked (congestion), blowing the nose or simple gentle cleaning of the nostrils is helpful.

For a sore throat, anything sucked or chewed in the mouth helps to stimulate saliva production which in turn eases the soreness of the throat. Similarly, warm fluids are helpful. Gargling with warm water with a little salt added may ease the soreness or a drink of warm water, lemon juice and honey may soothe the throat.

If a "productive" cough develops, cough suppressants should be avoided. Again, warm fluids may help. With a dry, non-productive cough, the main relief is to keep the throat lubricated. Cough suppressants should not be used for children; in adults, if the cough is severe or is disturbing sleep, then the use of a cough suppressant such as dextromethorphan may occasionally help.

If there are signs present that pneumonia has developed – fast breathing or chest indrawing – then medical attention and the use of an appropriate antibiotic are required (see box on page 98).

Health workers should make every attempt through better health education to discourage the use of drugs in the treatment of a simple cough or cold, but if a patient *insists* on a cough medicine, then health workers can recommend that parents make a safe, soothing preparation at home or can provide such a simple mixture for young children.

Table 5A-1
Cough and cold preparations with ineffective or potentially harmful ingredients in selected regions (1990-1991)

Country/Region	Number of preparations	No. with potentially harmful ingredients		No. with ineffective ingredients		No. with more than 3 ingredients	
		No.	%	No.	%	No.	%
Africa (July 1991)	97	51	52.6	83	85.6	27	27.8
Caribbean (Jan 1991)	68	46	67.6	59	86.8	20	29.4
Middle East (Dec 1990)	155	76	49.0	131	84.5	41	26.5
Pakistan (Mar-Aug 1990)	123	88	71.5	111	90.2	69	56.1
Totals all areas:	443	261	58.9	384	86.7	157	35.4

Sources: *Africa MIMS; Caribbean MIMS; Middle East MIMS; QIMP (Quick Index of Medical Preparations)* Pakistan

Conflicting claims

Companies will tell doctors almost anything to help sell cough medicines. In some cases, as these examples illustrate, the same company will use very different arguments – arguments that condemn some of their own products!

In March 1988 in Thailand, Parke-Davis ran an advertisement in the medical journal *Clinic* to promote its "new" cough medicine, Benadryl CD, highlighting the fact that one of its ingredients, codeine, is "among the most effective agents for suppressing cough". In May 1987, Parke-Davis ran an advertisement in another Thai journal, the *Siriraj Hospital Gazette*, for Benadryl Expectorant (which does not contain codeine) that claimed the product was "as effective as codeine" but did not have the "possible codeine complications". The introduction of the "new" product with codeine had little to do with improvements in health care.

In Pakistan in 1989, Sandoz distributed leaflets to doctors promoting its Triaminic syrup (which contains two antihistamines – pheniramine and mepyramine – and the nasal decongestant, phenylpropanolamine). The leaflets claimed that the "balanced formula" and "absence of unnecessary ingredients" led to an "absence of unwanted side effects". In other places, the leaflet claimed the product was one which "minimizes side effects" and that it was free from "unnecessary side effects". At the same time, doctors were also being circulated with leaflets promoting Triaminic-E as "the only safe, effective and most widely used expectorant". One of its selling points was that, because it only contained phenylpropanolamine and the supposed expectorant, guaifenesin, it avoided the antihistamine side effects and it also "saves the patient from side effects of shotgun therapies". In 1990, an advertisement for Triaminic-DM (phenylpropanolamine and dextromethorphan) in the *QIMP* prescribing guide also promoted the antihistamine-free benefits, describing the product as a "non-sedating cough suppressant". With all three of these products, the best way of avoiding side effects is to simply avoid the products.

In April 1990, an advertisement for Boehringer Ingelheim's Silomat (clobutinol) in *MIMS Middle East* made the point that, on the rare occasions when cough suppression was needed, "a simple preparation containing a single agent" was preferred. The ad went on: "The problem is many antitussives today also contain one or more additional agents like caffeine, antihistamines, analgesics, decongestants, anticholinergics, expectorants or even vitamins – the so-called cough cocktail. Most are either ineffective or contain inappropriate combinations which may be dangerous." This is good advice. Following it would effectively eliminate most of the cough medicines on the market – including Boehringer Ingelheim's own product, Abiadan, listed in the same issue of the Middle East prescribing guide. Abiadan contains orciprenaline, bromhexine and doxylamine – a sympathomimetic (decongestant), a mucolytic, and an antihistamine.

Recommendations for action

1. Governments should institute full reviews of the cough and cold preparations on the market – both prescription-only and over-the-counter drugs – with a view to:
   - removing those products containing potentially harmful ingredients, or those with more than three ingredients; and
   - eliminating those products which contain ineffective ingredients.
2. Governments, health authorities, and professional associations of doctors, pharmacists and nurses should develop accurate information for health workers and the general public advising them that there is no such thing as a cure for colds, and that the most effective treatment for the symptoms are: rest, plenty of warm liquids, and the *occasional* paracetamol to relieve aches or pain.

References:

1. Sperber, S.J. and Hayden, F.G., "Chemotherapy of Rhinovirus Colds", *Antimicrobial Agents and Chemotherapy*, Vol 32, No 4, April 1988, pp409-19
2. AMA, *Drug Evaluations*, (6th edn), Philadelphia, W.B. Saunders, 1986, p376
3. Lowenstein, S.R. and Parrino, T.A., "Management of the Common Cold", *Advances in Internal Medicine*, Vol 32, 1987, pp207-34
4. Hampson, N.B., Woolf, R.A. and Springmeyer, S.C., "Oral antibiotics for pneumonia", *Clinics in Chest Medicine*, Vol 12, No 2, Jun 1991, pp395-407
5. Lode, H., "Respiratory tract infections: when is antibiotic therapy indicated?", *Clinical Therapeutics*, Vol 13, No 1, Jan-Feb 1991, pp149-156
6. Anon., "Respiratory disease main cause of mortality in China", *Scrip*, No 1550, 19 Sep 1990, p22
7. von Schirnding, Y.E.R., Yach, D. and Klein, M., "Acute respiratory infections as an important cause of childhood deaths in South Africa", *South African Medical Journal*, Vol 80, 20 Jul 1991, pp79-82
8. Anon., *Childhood Pneumonia: strategies to meet the challenge*, (Proceedings of the First International Consultation on the Control of Acute Respiratory Infections, 1991), London, AHRTAG, 1992, p1
9. AMA, op cit, p376
10. Sperber and Hayden, op cit, pp410
11. Jackson, D.M. and Soothill, R., *Is the Medicine Making You Ill?*, North Ryde, Australia, Angus & Robertson, 1989, p29
12. Anon., "30% growth for OTC market", *Scrip*, No 1686, 24 Jan 1992, p19 (These figures refer to sales in the world's 15 largest markets.)
13. Anon., *OTC & Prescription Cough & Cold Products Market in the US*, New York, Frost and Sullivan, 1989; cited in: Anon., "US growth predicted for cold products", *Scrip*, No 1453, 6 Oct 1989, p19
14. Tan, M.L., *Dying for Drugs*, Quezon City, Health Action Information Network, 1988, p89
15. Po, A.L.W., *Non-Prescription Drugs*, (2nd edn), Oxford, Blackwell Scientific, 1990, p9
16. Anon., "UK OTC market worth £438 million in 1991", *Scrip*, No 1756, 25 Sep 1992, p3
17. Anon., "Self-medication products in Germany", *Scrip*, No 1773, 24 Nov 1992, p4
18. Berkowitz, R.R. and Tinkelman, D.G., "Evaluation of oral terfenadine for treatment of the common cold", *Annals of Allergy*, Vol 67, Dec 1991, pp593-7
19. Ahmad, S.R., "USA: Antihistamines in cold remedies", *Lancet*, Vol 339, 25 Apr 1992, p1045
20. Parish, P., *Medicines: A Guide for Everybody*, (6th edn, revised), London, Penguin, 1989, p101; Sperber, op cit, p414; AMA, op cit, p317; Reynolds, J.E.F. (ed.), *Martindale: The extra pharmacopoeia*, (29th edn), London, The Pharmaceutical Press, 1989, p444
21. Gilman, A.G., Rall, T.W., Nies, A.S., and Taylor, P. (eds), *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, New York, Pergamon Press, (8th edn) 1990, p587
22. Anon., "CSM on terfenadine/astemizole ADRs", *Scrip*, No 1777, 8 Dec 1992, p26
23. Chan, K. and Chan, G., "A study of prescribed H1-antihistamine preparations over a period of 12 months in community pharmacy", *Journal of Clinical Pharmacy and Therapeutics*, Vol 12, 1987, pp1-9
24. Parish, op cit, p100
25. Henry, J. (ed.), *The British Medical Association Guide to Medicines & Drugs*, London, Dorling Kindersley, (2nd edn) 1991, p89
26. Rylance, G. (ed.), *Drugs for children*, Copenhagen, WHO, 1987, p59
27. BMA and the Royal Pharmaceutical Society of Great Britain, *British National Formulary*, London, BMA and the Pharmaceutical Press, No 23, Mar 1992, p130
28. Parish, op cit, pp100-1
29. Orson, J. and Bassow, L., "Over-the-counter cough formulas", *Clinical Pediatrics*, Vol 26, No 6, June 1987, p287
30. Parish, op cit, p108; BMA and the Royal Pharmaceutical Society of Great Britain, op cit, p385
31. Anon., "Chloraseptic throat spray ADR warning", *Scrip*, No 1524, 20 Jun 1990, p31
32. Parish, op cit, pp104-5
33. Harris, M.F. and Fisher, R.R., "Management of acute lower respiratory infections", *Medical Journal of Australia*, Vol 155, 21 Oct 1991, pp538-46
34. Parish, op cit, p103
35. Phelan, P., "How the experts manage mild ARI", *ARI News*, No 8, Aug 1987, p2
36. Parish, op cit, p103
37. BMA and the Royal Pharmaceutical Society of Great Britain, op cit, p129
38. Parish, op cit, p104
39. Lowenstein and Parrino, op cit, p221
40. BMA and the Royal Pharmaceutical Society of Great Britain, op cit, p127
41. Ibid, p128
42. Korppi, M., Laurikainen, K., et al, "Antitussives in the treatment of acute transient cough in children", *Acta Paediatrica Scandinavica*, Vol 80, 1991, pp969-71
43. AMA, op cit, pp374-5
44. WHO, *The Use of Essential Drugs: fourth report of the WHO expert committee*, (Technical Report Series No 796), Geneva, WHO, 1990
45. AMA, op cit, pp374-5
46. BMA and the Royal Pharmaceutical Society of Great Britain, op cit, p129
47. Lowenstein and Parrino, op cit, p218
48. AMA, op cit, p385
49. Chetley, A., *Peddling Placebos: An analysis of cough and cold remedies*, Amsterdam, HAI, 1990, p5
50. Sundararaman, T., "Essential Vs. Irrational Drugs", in *A Decade After Hathi Committee*, (Ekbal, B., ed.), Sivakashi, India, Kerala Sastra Sahitya Parishat, 1988, p199
51. BMA and the Royal Pharmaceutical Society of Great Britain, op cit, pp1128-31
52. Anon., "New guide to OTC medicines in France", *Scrip*, No 1715/16, 6/8 May 1992, p8
53. *ARI News*, No 8, 1987, p1
54. Anon., *Childhood Pneumonia...*, op cit, p12
55. Ibid

Chetley, A. *Problem Drugs*, Amsterdam,
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Swatting the symptoms of malnutrition

Malnutrition is a daily reality for as many as a billion people – nearly one-fifth of the world's population. According to World Bank statistics, women and children account for 80% of malnourished people.[1] Malnutrition affects more than 500 million children in developing countries according to the World Health Organization (WHO).[2] As many as 8.5 million deaths a year of children under five can be attributed to malnutrition. Millions more children survive on the edge of starvation.[3]

If malnutrition is not checked, children who do not die are likely to be permanently handicapped, both physically and mentally. "Malnutrition impairs the physical and mental development of children and the working and earning capacity of adults; it is therefore a cause as well as a consequence of poverty."[4]

This waste of human potential begins early in life, sometimes even before birth. Maternal malnutrition during pregnancy and lactation is one factor linked to children's failure to grow (stunting).[5] Poor mental development in stunted children is at least partly attributable to undernutrition.[6] Because 80% of the development of the human brain occurs before birth and during the first two years after birth, malnutrition of the mother during (or before) pregnancy or of the child after birth can harm the development of the child's brain.[7]

One-third of babies born in developing countries weigh less than 2,500 grams. Preventing low birth weight, by improving the nutritional health of women and girls, and by ensuring more food and rest in pregnancy, will reduce the risk of malnutrition.[8] Low-birth-weight infants are less likely to grow well, more likely to fall ill, and four times more likely to die in the first year of life than babies of normal weight.[9]

Malnutrition and disease

Malnutrition and disease work together synergically, especially in children.[10] Malnutrition lowers resistance to infectious disease, so that a child is more likely to be infected and the disease is more prolonged, more severe, and has more complications. But also, *all* infections have a nutritional impact. Infections can decrease the body's absorption of nutrients. They can induce rejection of food by vomiting. They can drain away nutrients through diarrhoea. They can induce mothers to stop feeding while the diarrhoea lasts. And by any or all of these methods, infections can lead to decreased rates of child growth and impaired appetite.[11]

In any child, growth is the most important single indicator of health. If a child is regularly putting on weight every month, there is unlikely to be anything fundamentally wrong.[12]

Loss of appetite is a common symptom of illness. It is important to encourage children who are ill to take food and drink in small amounts regularly. Even when

young children (under three) are well, because their stomachs are small, they should eat small amounts of food high in energy five or six times a day.[13]

Missing the mark

Klaus Leisinger, Head of International Relations at Ciba-Geigy, makes the point that "there are no specific preventive measures for illnesses that arise from poverty".[14] However, that has not stopped the pharmaceutical industry from promoting a wide range of products to do what has been called "symptom swatting" – focusing on ways of dealing with the symptoms, rather than treating the underlying causes.[15] The symptoms of malnutrition are easy to identify – poor growth, loss of appetite, impaired mental development, tiredness and fatigue. The products – appetite stimulants, anabolic steroids, brain tonics, and vitamins – are almost always inappropriate, sometimes harmful, and a waste of scarce resources.

The use of these medicines for the "treatment" of conditions resulting from malnutrition has to be strongly condemned. One researcher examining the promotion of anabolic steroids said, "the promotion of a drug which so blatantly exploits parents' concern for their children – claiming it helps them to put on weight in countries where undernutrition and/or infection are invariably responsible for a failure to thrive – is one of the least creditable of all the examples of dangerous promotion".[16]

Primary health care specialist John Macdonald makes clear the chain of events and exploitation that lead to the ineffective use of drugs for conditions of malnutrition:

> "Poor, underfed people, suffering from diseases of poverty and a general situation of marginalisation, frequently believe that they have to spend what little money they have on drugs in an often desperate effort to keep their families alive.... If blame is to be laid at anyone's door, it should not be at that of the mother but at the door of those who exploit her poverty for their own profit. Neither can we pass by the door of those health workers who are happy to leave intact and unchallenged the medical model of health care with its emphasis on drugs because their interests are served by the existing situation."[17]

In the long term, the problems of malnutrition and hunger can be solved only through improvements in the social and economic conditions of the world's poor. A World Bank study concludes: "Many people do not have enough to eat, despite there being food enough for all. This is not a failure of food production, still less of agricultural technology. It is a failure to provide all people with the opportunity to secure enough food – something that is very hard to do in low-income countries."[18]

Alan Berg, the World Bank's nutrition adviser, stresses that "the poorest cannot wait. A direct attack on malnutrition is needed as well, and governments willing to make that effort now have effective and affordable measures to make it happen."[19]

Some of the interventions that deal with the interlinked causes and effects of poverty and malnutrition include preventing measles, tuberculosis, and whooping cough; encouraging breastfeeding; treating pneumonia and diarrhoea at an early stage; and reducing undernutrition before birth. Dr Edgar Mohs, former Minister of Health of Costa Rica, explains some lessons that have been learned in his country:

> "In the past, we believed that the lack of food was a major cause of illness and malnutrition. We have now started to accept that family spacing, breastfeeding, and the control of infectious disease are the keys to eradication."[20]

Overall, UNICEF has found that, in several regions of the world, child malnutrition can be cut in half at a cost of only US $10 per child per year.[21] Ironically, the cost of one course of Sandoz's appetite stimulant, pizotifen, also comes to about $10.[22]

Appetite stimulants: more harm than good

> "I cannot clearly recall *any* occasion on which I considered that an appetite stimulant drug was indicated. Furthermore, in practice in developing countries (where I spent 20 years) the indiscriminate use of appetite stimulants that have powerful and potentially dangerous pharmacological properties in children whose failure to thrive usually reflects lack of food and often is caused by underlying diseases like tuberculosis, is in my view *contraindicated* and probably unethical."
> – *Professor of Tropical Paediatrics*[23]

In 1985, the UK-based organisation, Social Audit, launched an international campaign to halt the unethical promotion of appetite stimulants for hungry children in developing countries. At the time, Social Audit's director, Charles Medawar, described appetite stimulants as "a complete irrelevance" and "a waste of money".[24]

Promoting the side effect

The two leading products – Mosegor (pizotifen) by Sandoz, and Periactin (cyproheptadine) by Merck Sharp & Dohme (MSD) – have one thing in common: they both tend to increase appetite and promote weight gain in *some* patients, as a side effect. Cyproheptadine is an antihistamine which can be used to treat allergic reactions such as itchiness or

skin rashes. Pizotifen is also an antihistamine but is generally used in the prophylaxis and treatment of migraine or vascular headaches.

Cyproheptadine may initially lead to some increase in appetite and weight gain, but the result is short-lived. The American Medical Association (AMA) says that "although the results of several studies suggest that cyproheptadine stimulates linear growth and weight gain in children, this effect is inconsistent, transient, and quickly reversible after withdrawal of the drug."[25]

The British Medical Association describes weight gain as a result of appetite stimulation as "the main disadvantage of prolonged use of pizotifen."[26]

Both drugs also have undesirable side effects, the most common being a tendency towards drowsiness, which "may be troublesome" with pizotifen. Other side effects of both drugs include: inability to concentrate, dizziness, hypotension, weakness, nausea, vomiting, diarrhoea, constipation, headache, blurred vision, irritability, nightmares, anorexia, dryness of the mouth, tightness of the chest, and weakness in the hands.[27]

Uncertain efficacy and a wide range of possible side effects throws into doubt the usefulness of either drug. As a leading textbook on clinical pharmacology points out, "in general, little or nothing is gained by stimulating appetite by drugs."[28]

Finding the cause

Loss of appetite (anorexia) in a child may be temporary and not require any treatment. When loss of appetite is serious, it is important to identify and treat the cause – that is, whatever led to the loss of appetite. In children, this may include: malnutrition, infections, emotional deprivation, malabsorption, heart failure, renal/central nervous system/endocrine disorders, chronic inflammation, genetic disorders and malignancies. In adults and the elderly anorexia with weight loss may be caused by any of a similarly long list of medical conditions.

In extreme cases of malnutrition or anorexia nervosa, use of appetite stimulants may be dangerous. Loss of appetite due to food shortage should be treated by gradually increasing the amount of food.[29]

A professor of pharmacology concludes: "I do not believe that there is a role for appetite stimulants of the cyproheptadine or pizotifen type in medical practice, be it in the developed world or Third World countries."[30]

Double standards

In the USA in 1971, the *Medical Letter* noted that:

> "multiple page advertisements of cyproheptadine in current medical journals picture an attractive child devouring a large meal to the apparent delight of his attentive mother. This advertising will probably encourage widespread pediatric use of cyproheptadine.... Although cyproheptadine stimulates appetite in some children, *Medical Letter* consultants believe that promotion of the drug as an appetite stimulant will do more harm than good."[31]

In the same year, the US Food and Drug Administration (FDA) considered the evidence for using cyproheptadine as an appetite stimulant to be inadequate, and MSD stopped promoting it for this indication in the USA. It is "not recommended" as an appetite stimulant by the *British National Formulary*.[32]

However, in 1991, Periactin was still listed in *MIMS Africa* as "an appetite stimulant where, in the opinion of the physician, increased food intake is desirable and an adequate diet is available."[33] MSD told Social Audit in 1986 that it would no longer promote cyproheptadine as an appetite stimulant. Nonetheless, the company maintained that appetite stimulation was a "well established and medically valid" indication for use.[34]

In 1985, Sandoz told Social Audit that it would withdraw all promotional material for Mosegor (pizotifen) and have it redesigned at headquarters level. When the new material emerged in countries such as Pakistan in 1987, there was very little change. The promotional material simply stressed that "loss of appetite can be a symptom of many clinical and surgical conditions" and suggested pizotifen as a means of helping to deal with it.

In 1991, in the Philippines, pizotifen was still being advertised as an appetite stimulant.[35] In 1991, in Pakistan, appetite stimulants were the fourth largest category of drugs. MSD and Sandoz were both selling their products, as were several other companies including High Noon Labs with its cyproheptadine preparation, Tres-orix Forte. Following discussions with paediatrician Prof. T.I. Bhutta, High Noon agreed to withdraw its product. However, it had not yet been withdrawn by the end of 1992. Sandoz agreed to withdraw Mosegor-V (pizotifen and vitamins) and, once again, to modify its product information for Mosegor.[36]

Other ingredients

Traditional remedies for loss of appetite include preparations containing simple and aromatic bitters such as alkaline gentian mixture. The *British National Formulary* says they "all depend on suggestion".[37]

These preparations sometimes include vitamins, as do some brands of pizotifen and cyproheptadine. The vitamins do not add to the usefulness of these products, despite claims to the contrary. Similarly, many

multivitamin products often include as one of their indications "loss of appetite" as well as other associated conditions such as weakness, tiredness, and physical or mental strain. However, their use for these symptoms is not supported by any firm scientific evidence. Other food substances, such as amino acids, are also sometimes included with cyproheptadine. Wallace Pharmaceuticals advertised its Cyprowal syrup with cyproheptadine and lysine (an amino acid) in India in 1989 as a product that "builds up appetite, adds nutritional value and helps children gain weight".[38]

Drugs to stimulate appetite are more than just a waste of resources. A WHO publication points out that "these preparations should not be used."[39] They cause harm by diverting attention away from the real causes of poor growth and development, and replace this with the idea that a drug is the answer.

Anabolic steroids: of no use?

Anabolic steroids are also often promoted (incorrectly) as appetite stimulants. The Dutch company, Organon, controls at least half the world market for anabolic steroids – synthetic derivatives of the male sex hormone, testosterone. The main anabolics are: ethylestrenol, methandienone, nandrolone, oxymetholone and stanozolol.

Testosterone has both an androgenic effect – it stimulates the development of the male sex organs and male secondary sexual characteristics such as beard growth and deepening of the voice – and an anabolic effect, stimulating protein synthesis and the growth of body tissues such as muscles, bones and blood.

The primary use for androgens is to deal with impaired functioning of the testes (hypogonadism). Because androgens have significant effects on muscle mass and on body weight when given to hypogonadal men, it was assumed, but never proven, that they could promote growth of muscle above normal levels. This assumption was based upon the belief that anabolic and androgenic actions are different, and a concerted effort was made to devise pure anabolic steroids that have no androgenic effects. However, "all anabolic hormones tested to date are also androgenic."[40]

The use of anabolic steroids in children may actually stunt their growth.[41] The AMA says that "anabolic steroids should not be used to stimulate growth in children" because they can cause the bones to stop growing at an earlier age than normal.[42]

In 1983, the Dutch group, WEMOS (Working Group on Health and Development Issues) complained to the Association of Dutch Pharmaceutical Industries (NEFARMA) about Organon's promotion of anabolic steroids in developing countries. WEMOS said Organon was promoting its anabolic steroids to "stimulate appetite", "improve normal growth" and "increase body weight" among children. One advertisement from India talked about offering children who used the product "a life full of fun and frolic".

NEFARMA ruled in January 1984 that "Organon had not exercised sufficient care" in its marketing practices. NEFARMA commented on the "significant differences" between product literature in the Netherlands and that used in developing countries, saying that "this could result in users, particularly children, being at risk." Organon accepted NEFARMA's findings, and announced that "corrective action has been taken".[43]

Slow to change

However, Organon was slow to change. WEMOS carried out a survey in 1987 and found evidence that the company was still promoting anabolics for children and for a wide range of dubious indications in adults.[44] The survey found that in 23 prescribing guides, there was an average of five indications that lacked scientific validity (range: 2 to 14). A total of 26 package inserts from three formulations in 14 countries also contained an average of five indications that lacked scientific validity (range: 1 to 8). Organon responded that it was doing its best to ensure that the information in all prescribing guides and product information conformed to its own guidelines on the use of anabolic steroids (which themselves contained six indications that lacked evidence of validity).

Unlikely uses

Among these unlikely uses are convalescence, osteoporosis, breast cancer, and management of kidney failure. Anabolic steroids have been found to be "ineffective" at building up body protein during convalescence after major surgery or a severe accident and for treating patients with chronic debilitating diseases.[45] A nutritious diet high in protein is more effective at enabling the body's own mechanisms to control the required build-up of protein.[46] The virilising side effects and lack of evidence of efficacy of "anabolics" rules them out for the treatment of postmenopausal women with osteoporosis.[47]

Goodman and Gilman's pharmacology textbook notes that "androgens do not play a major role in the management of carcinoma of the breast", and that they are "of little value in the management of nitrogen accumulation in chronic renal failure; at best they induce a transient improvement in nitrogen balance that is of doubtful importance. In acute renal failure... patients do well without androgen therapy." They add that "androgens have a minor role in treatment of the anaemia of renal failure.... Whether the benefits of such treatment outweigh the potential adverse effects is unclear."[48]

Adverse effects

Adverse effects with anabolic steroids can be severe. In addition to the side effects already noted – the

problems of masculinisation in women and stunted growth in children – anabolic steroids can also cause feminising side effects in men. The reason for this is poorly understood, but the effects are particularly severe in children.[49]

Anabolic steroids are associated with "a long list of potentially toxic effects". In particular, they can cause benign and malignant liver tumors, and a rare, but dangerous condition called peliosis hepatis which leads to blood-filled cysts in the liver that can suddenly rupture.[50] This, and other liver damage, is particularly liable to occur with the use of the 17-alpha-alkylated steroids such as ethylestrenol, oxymetholone, methandienone, danazol and stanozolol. Experts now agree that the potential for the development of these serious side effects means that these steroids should be avoided "in almost all circumstances with the possible exception of hereditary angioneurotic oedema" (a rare allergic condition producing swelling of the skin and severe itching), or for life-saving treatment such as aplastic anaemia.[51]

Danazol is also extensively used in the treatment of endometriosis, a condition in which the type of tissue lining the womb is found at other sites within the pelvic cavity. However, it may not be of any benefit to women with mild endometriosis; endometriosis may recur after treatment; and it is "considerably more expensive" than therapeutically equivalent courses of other medication.[51a]

The effects on the liver have not been reported with injectable testosterone esters. Thus, in all cases where androgen therapy is legitimately indicated, "testosterone esters are the preferred agents."[52]

Anabolics and athletic performance

A major, although generally illegal, use of anabolic steroids is among athletes to enhance performance. In highly competitive situations, for example among high school students in the USA where the ability to excel at a sport might mean winning a scholarship to attend university, nearly 7% of male students in their final year have used anabolics, two-thirds of them began using them before the age of 16.[53] However, "appropriately controlled studies of the effects of androgens on strength and performance in conditioned athletes have yielded inconclusive results".[54] The AMA says such use of anabolic steroids is "contrary to the ethical principles of athletic competition and is deplored." It adds that not only is this "a medically trivial indication", but adverse effects are likely to occur.[55]

A limited market

A survey carried out in 1988 found that many of the "anabolics" manufacturers had begun to get the message about the need to convey more warnings against the use of their products in children and to advise against use by athletes.[56] However, in 1990 and 1991, companies were still promoting anabolic steroids for a variety of unproven indications such as: osteoporosis, debility, senility, kidney disease, muscular dystrophy, and convalescence.[57] Stronger measures could be taken. The scientific evidence suggests that many of the anabolic steroids currently on the market have no use whatsoever – particularly those liable to cause liver damage – and the remainder have only a very limited role to play in therapy.

[See also the sections on *Brain Tonics* and *Vitamins*.]

Recommendations for action

Continuing to waste resources on ineffective and inappropriate drugs is not the answer to problems of malnutrition. The solutions are more likely to lie in efforts to:

1. concentrate available resources on strengthening the primary health care infrastructure, including the supply of essential drugs and vaccines for common infections which exacerbate malnutrition or are made much more dangerous by existing malnutrition.

2. eliminate wasteful expenditure on drugs which, at best, attempt to deal only with the symptoms of malnutrition and, at worst, are ineffective or dangerous;

3. introduce licensing restrictions and promotional controls on products such as appetite stimulants, brain tonics, anabolic steroids, and vitamin preparations. These should include:
   - a ban on all anabolic steroids with a potential for causing serious liver damage – with the exception of stanozolol and danazol products which should be removed from the general market and severely restricted to hospital use only by specialists for indications such as hereditary angioneurotic oedema, aplastic anaemia, or serious cases of endometriosis;
   - restricting the use of the remaining anabolic steroids – such as nandrolone – to hospital-based specialists as an experimental drug for the treatment of unresponsive anaemias;
   - an end to all forms of promotion of appetite stimulants and their removal from the general market.

References:

1. Seitz, I.L., *The Politics of Development*, New York, Basil Blackwell, 1988, p47
2. Latham, M.C., "Protein-energy malnutrition – its epidemiology and control", *JEPTO*, Vol 10, No 4-5, Jul-Oct 1990, pp168-180
3. Anon., "The backdrop of poverty, disease and debt", *New Scientist*, 17 Feb 1990, p41
4. UNICEF, *The State of the World's Children 1990*, Oxford and New York, Oxford University Press, 1989, p27
5. Kusin, J.A., Kardjati, S., et al, "Energy supplementation during pregnancy and postnatal growth", *Lancet*, Vol 340, 12 Sep 1992, pp623-6
6. Grantham-McGregor, S.M., Powell, C.A., et al, "Nutritional supplementation, psychosocial stimulation, and mental development of stunted children: the Jamaican study", *Lancet*, Vol 338, 6 Jul 1991, pp1-5
7. Seitz, op cit, p52
8. UNICEF, *The State of the World's Children 1991*, Oxford and New York, Oxford University Press, 1990, p10
9. UNICEF, WHO and UNESCO, *Facts for Life: A Communication Challenge*, New York, UNICEF, 1989, p5
10. Macdonald, J.J., *Primary Health Care: medicine in its place*, London, Earthscan, 1993, p21
11. Pryer, J. and Crook, N., *Cities of Hunger: urban malnutrition in developing countries*, Oxford, Oxfam, 1988, p11
12. UNICEF, 1989, op cit, p31
13. UNICEF, WHO and UNESCO, op cit, pp28-9
14. Leisinger, K.M., *Poverty, Sickness and Medicines: an unholy alliance?*, Geneva, IFPMA, 1989, p23
15. Kennedy, I., *The Unmasking of Medicine*, London, Paladin, 1983, p23
16. Muller, M., *The Health of Nations*, London, Faber & Faber, 1982, p35
17. Macdonald, op cit, p46
18. Cited in: McKeown, T., "The road to health", *World Health Forum*, Vol 10, No 3/4, 1989, pp408-16
19. UNICEF, 1989, op cit, p29
20. UNICEF, *The State of the World's Children 1989*, Oxford and New York, Oxford University Press, 1988, p46
21. UNICEF, 1990, op cit, p10
22. Medawar, C. and Gilbert, D., *Double Standards*, London/The Hague, Social Audit/IOCU, 1985
23. Daniel, T., *Appetite Stimulants for Children in Developing Countries? Experts say DON'T!*, London, Social Audit, 1986, p2
24. Social Audit, press release, *Social Audit Calls For Withdrawal of Appetite Stimulants*, London, 24 June 1985
25. AMA, *Drug Evaluations*, Chicago, (5th edn) 1983, p1478
26. Henry, J. (ed.), *The British Medical Association Guide to Medicines & Drugs*, London, Dorling Kindersley, (2nd edn) 1991, p346
27. Reynolds, J.E.F. (ed.), *Martindale: The Extra Pharmacopoeia*, London, The Pharmaceutical Press, (29th edn) 1989, pp443, 451, 458-9
28. Laurence, D.R. and Bennett, P.N., *Clinical Pharmacology*, Edinburgh, Churchill Livingstone, (6th edn), 1987, p365
29. Medawar and Gilbert, op cit, p2
30. Daniel, op cit, p2
31. Anon., "Cyproheptadine (Periactin)", *The Medical Letter on Drugs and Therapeutics*, Vol 5, No 3, 5 Mar 1971
32. BMA and the Royal Pharmaceutical Society of Great Britain, *British National Formulary*, London, BMA and The Pharmaceutical Press, No 23, Mar 1992, p122
33. *MIMS Africa*, Jul 1991, p106
34. Anon., "Merck & Co stops promoting Periactin", *Scrip*, No 1101, 12 May 1986, p7
35. Quijano, R., "Vitamins, tonics and appetite stimulants", *The Drug Monitor*, Vol VI, No 8/9, Aug/Sep 1991, pp74-7
36. Anon., "Appetite stimulant withdrawn", *HAI News*, No 61, Oct 1991, p3; Anon., *HAI International Meeting Report*, Amsterdam, HAI-Europe, 1993, p11
37. BMA and the Royal Pharmaceutical Society of Great Britain, op cit, p344
38. *CIMS*, Sep-Dec 1989, p12
39. Rylance, G. (ed.), *Drugs for children*, Copenhagen, WHO, 1987, p48
40. Gilman, A.G., Rall, T.W., Nies, A.S., and Taylor, P. (eds), *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, New York, Pergamon Press, (8th edn) 1990, pp1423-7
41. Ibid
42. AMA, *Drug Evaluations*, Philadelphia, W.B. Saunders Co., (6th edn) 1986, pp680-1, 699
43. IFPMA, *IFPMA Code of Pharmaceutical Marketing Practice: Status Report March 1984*, Geneva, IFPMA, Apr 1984, p3
44. WEMOS, *Organon and anabolic steroids*, Amsterdam, 1987, p6
45. Gilman, et al, op cit
46. Parish, P., *Medicines: a guide for everybody*, London, Penguin (6th edn, revised), 1989, p226
47. AMA, 1986, op cit, pp680-1, 699
48. Gilman, et al, op cit
49. Ibid
50. Dukes, M.N.G. and Beeley, L., (eds), *Side Effects of Drugs Annual 14*, Amsterdam, Elsevier, 1990, p360
51. Gilman, et al, op cit; Dukes and Beeley, op cit
51a. AMA, op cit., pp 741-2 and 74708.
52. Gilman, et al, op cit
53. Geddes, J.A., "Anabolic steroids and the athlete", *Canadian Family Physician*, Vol 37, Apr 1991, pp979-83
54. Gilman, et al, op cit
55. AMA, 1986, op cit, pp680-1, 699
56. Silverman, M., Lydecker, M. and Lee, P.R., *Bad Medicine: the prescription drug industry in the Third World*, Stanford, Stanford University Press, 1992, pp39-40, 313, 315
57. See: *MIMS Africa*, Jan 1991, p140; or *MIMS Middle East*, Dec 1990, p140, for example.

Chetley, A. *Problem Drugs*, Amsterdam,
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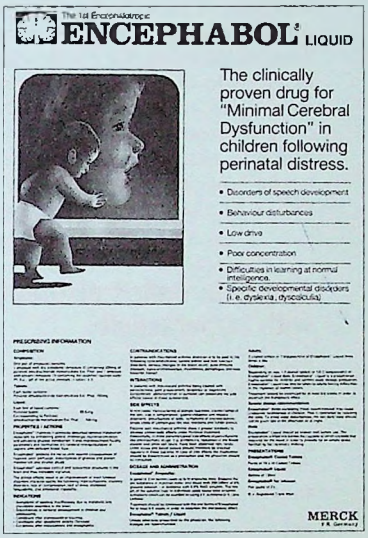
6B. Brain tonics

Drugs in search of a disease

Two types of people feature prominently in advertising for drugs designed to deal with "brain disorders": children who suffer from lack of attention, poor performance at school, and hyperactivity; and the elderly who suffer from loss of memory, dementia, depression. In both cases, the claims for the drugs suggested for treatment stretch medical findings far beyond acceptable limits. That has not stopped a third group of people – students of all ages who need to concentrate and an increasing number of young business people – from turning to medicines in the hope that drugs will help improve their concentration and memory power.



Merck advertises Encephabol in Pakistan, May 1989

From cradle to grave

The German company, E. Merck, was promoting its "brain tonic", Encephabol (pyritinol), in Pakistan in 1989 as "The clinically proven drug for 'Minimal Cerebral Dysfunction' in children following perinatal distress". The illustration used on the promotional leaflet showed a baby taking his first steps. Similar promotion in Sri Lanka in 1991 advocated the use of the drug for neonates.

In 1990 in Pakistan, Swiss-based Sandoz was selling its "brain tonic", Hydergine (co-dergocrine mesylate), as a product to improve "dizziness, forgetfulness and concentration problems" among the elderly. "Put life back into their life" proclaimed the advertisement in a prescribing guide. The illustration in the ad showed a group of elderly men obviously enjoying life.

Hydergine for the elderly: in QIMP, Pakistan, 1990

In 1991, in Uruguay, French-based Roussel (a subsidiary of the German company, Hoechst) ran public advertising in a newspaper proclaiming that its "brain tonic", Targifor (arginine aspartate), would help students pass their exams because it "increases concentration, increases intellectual output".[1] In 1988 in Brazil, Roussel's advertising to doctors for Targifor also promoted the drug for "intellectual fatigue", but added the even more dubious claim that it would deal with "sexual fatigue".

These examples illustrate the broad range of potential sales for companies marketing "brain tonics" or "cognitive enhancers". Estimates suggest that the market in the USA alone will be worth more than $20 million a year by 1994.[2] There are more than 160 "cognitive enhancers" in development worldwide. Professor Ian Hindmarch, from the Human Psychopharmacology Research Unit at the University of Surrey in the UK, describes the pharmaceutical industry's efforts to put a large number of drugs on the market for people who are growing old as little more than a way of "printing money".[3] With more than 50 million people worldwide over the age of 65 currently estimated to be suffering from dementia, analysts predict that the worldwide market for "cognitive enhancers" to treat dementia will be over $1.5 billion by the year 2000.[4]

"In this case...", Roussel makes dubious claims for arginine aspartate (Targifor) in Ars Curandi, Brazil, Oct 1988

Attention deficit disorder with hyperactivity

But as E. Merck's efforts to sell Encephabol demonstrate, the entry point for "cognitive enhancers" is often with children, although the credit for the process of creating a market for a not very well specified disease condition should probably rest with another company, Ciba-Geigy.

In 1961, Ciba-Geigy proposed that its amphetamine-like drug, Ritalin (methylphenidate), should be used to treat functional behavioural problems in children. Initially rejected by the US Food and Drug Administration (FDA), it was approved for this use in 1963. In the same year, a task force was formed in the USA to define a previously unrecognised patient: the child with Minimal Brain Dysfunction (MBD). By 1966, the task force was able to produce a definition that included 99 symptoms that can cause learning difficulties, ranging from too little to too much activity. The head of the task force, Dr S. Clements, subsequently worked as a consultant for Ciba-Geigy and produced the company's handbook for doctors on MBD.[5] These efforts were backed with a concentrated "push" on selling the drug and the condition. Sales representatives were told in a 1971 sales report that their "ingenuity" in promoting the syndrome and the product was paying off as doctors themselves began to talk about the behavioural disorder.[6] By 1975 around one million US children were diagnosed as suffering from MBD. Of these, 515,000 were treated with drugs; 265,000 were given Ritalin.[7]

In 1980, the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-III) of the American Psychiatric Association rejected the term minimal brain dysfunction in favour of either "attention deficit disorder with hyperactivity, attention deficit disorder without hyperactivity, and attention deficit disorder, residual type (hyperactivity is no longer present but attention deficit and impulsiveness persist)."[8] The term that has tended to stick is attention deficit disorder with hyperactivity (ADDH) and about 3-6% of school age children in the USA are currently believed to be taking medication for the disorder,[9] despite some doubt as to whether it is actually a disease, and if so, whether drug therapy is the answer.

Although drugs such as methylphenidate may improve short-term learning in some children initially, "no data are available to demonstrate conclusively that they improve learning for long periods. Follow-up studies indicate that these children may continue to have difficulty in school, exhibit behavioural disorders, and have poor self-esteem into adolescence or even into adulthood."[10] Generally, 70-80% of children who had ADDH continue to have significant problems in adolescence.[11] Although treatment with amphetamine-type drugs may produce clinical improvement, it does not seem to affect selective attention. This suggests that psychostimulants alone are not sufficient.[12] Because there are multiple factors that are implicated in ADDH, "it is unlikely that a 'cure' or even a mode of prevention will be found".[13]

In any event, the use of methylphenidate is not recommended by the World Health Organization (WHO), at least not in general practice, "because of the frequency and severity of its adverse effects". These include loss of appetite, weight loss, growth inhibition, tearfulness, irritability, insomnia and personality change such as disorientation, aggression and paranoid psychosis.[14] Some of these conditions are those that methylphenidate is supposed to ameliorate.

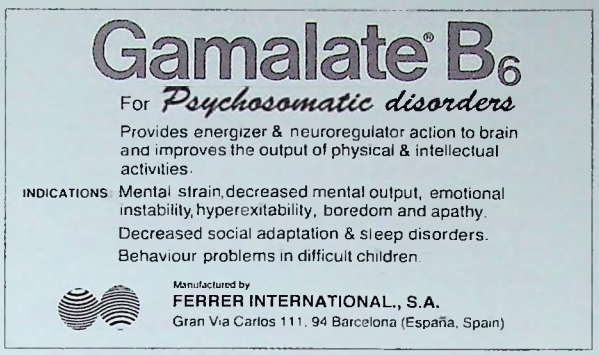
No scientific evidence

If there is a dispute about whether to use methylphenidate or other amphetamine-like drugs for children with learning and behavioural disorders, there should be no dispute about E. Merck's Encephabol (pyritinol). Pyritinol is derived from, and has a similar chemical composition to, vitamin B6, although in animal tests it has been shown to possess no vitamin B6 action. According to E. Merck, pyritinol improves blood supply to the brain and also alters the metabolism of the nerve cells so that oxygen consumption and glucose uptake improves.[15] However, despite all the claims made by Merck, and despite the drug having been available for some 30 years, it fails to get even a mention in authoritative texts on pharmacology and therapeutics such as *Goodman and Gilman's The Pharmacological Basis of Therapeutics* or the AMA's *Drug Evaluations*. WHO points out that the effectiveness of pyritinol "has not been demonstrated".[16] In 1988, the Medical Lobby for Appropriate Marketing (MaLAM) was unable to find a single published clinical trial of the efficacy of pyritinol "for any indication".[17]

A British doctor with considerable experience in developing countries wrote in *The Lancet*: "There is no scientific evidence for this drug's efficacy. I have seen this drug prescribed for children with various disabilities, including cerebral palsy, mental retardation, epilepsy, and learning and behavioural problems, in Syria, India, Sri Lanka, Malaysia, Singapore, and Indonesia."[18] A recently published survey of 1988 prescribing guides found Encephabol and other pyritinol products being promoted for children in India, Indonesia, Thailand, Malaysia, Singapore, the Philippines, Mexico, and Venezuela.[19]

"Cerebral" vasodilators

Merck also promotes pyritinol as a treatment for senile dementia, making much of the supposed benefit of increasing the blood flow to the brain. This argument is based on outdated theories that attributed the cause of senile dementia to inadequate blood flow to the brain. Although this explanation has been discredited, it gave rise to a number of "cerebral" vasodilators and similar drugs (often called nootropics) that are still currently in wide use for the treatment of mental failure in the elderly. These include products such as nicotinic acid derivatives, nicergoline, oxpentifylline, thymoxamine, co-dergocrine mesylate, cyclandelate, piracetam, buflomedil, cinnarizine, flunarizine, and the calcium channel blocker, nimodipine.



A cure for boredom and emotional instability (among other things): Gamalate B6, in QIMP, Pakistan, 1990

One expert notes that:

> "No drug has a special effect upon the blood vessels which supply the brain. Those that are used are general vasodilators. Their effectiveness in treating disorders produced by changes in the arteries supplying the brain, though of help in some patients, has never been clearly evaluated because of the complexities involved. Furthermore, there are risks involved in the use of such drugs – fall in blood pressure and redistribution of blood supply away from areas that may require more oxygen as the result of an already diminished blood supply."[20]

Goodman and Gilman's pharmacology textbook says "the case for clinical efficacy is unimpressive" for these products in treating dementia.[21] According to the *British National Formulary* (BNF), "these drugs are claimed to improve mental function. Some improvements in performance of psychological tests have been reported but the drugs have not been shown clinically to be of much benefit in senile dementia."[22]

Nonetheless, products such as these are widely promoted, particularly in developing countries, for a range of symptoms associated with dementia and old

age. Dr J.L.T. Birley, a British doctor, wrote in *The Lancet* of the shock of finding misleading advertising for "brain tonics" when he attended a conference in Pakistan in late 1988. US-based Abbott claimed its buflomedil (Loftyl) "alleviates symptoms of intellectual deterioration, change of personality, and loss of memory", while Farmitalia Carlo Erba's nicergoline was indicated for "memory disorders, reduced concentration, mood depression, unsociability, loss of self-care, asthenia [weakness], anorexia [loss of appetite], and dizziness".[23]

MaLAM has regularly challenged pharmaceutical companies to defend the claims made for the various "brain tonics" on the market (see Table 6B-1). To date, the industry has been unable to produce much evidence in its defence. Where companies have responded to MaLAM, the quality of the studies they have used to justify their claims has generally been poor.[24]

Milton Silverman and his colleagues documented a vast array of similar claims for products containing piracetam, bencyclane, buflomedil, cinnarizine, co-dergocrine, flunarizine, oxpentifylline (pentoxifylline), and pyritinol made during 1987-88 in Africa, Brazil, Caribbean, Central America, Colombia, Ecuador, India, Indonesia, Malaysia, Mexico, Middle East, Peru, Philippines, Singapore, Thailand, and Venezuela.[25]

Two of these products warrant additional comment – flunarizine and ergoloid mesylates such as co-dergocrine. Flunarizine illustrates the need to use caution with drugs of this type because of their possible risks, and co-dergocrine illustrates the difficulty of proving efficacy of these drugs and the need to take company claims with a large dose of scepticism.

Flunarizine

When MaLAM carried out a literature search, it failed to turn up "any convincing evidence for using flunarizine for any indication. Flunarizine appears to be both useless and harmful. New evidence has shown it to be a cause of Parkinsonism and depression."[26] Concern about the lack of efficacy of flunarizine and its potential for serious side effects led the German drug regulatory authority (BGA) in 1991 to restrict the indications for the product to vestibular vertigo only. The BGA said there have been "no studies using methods appropriate to produce adequate measurements of the effect of flunarizine on cerebral blood flow. From the clinical studies available there is insufficient proof of efficacy for flunarizine in the treatment of disorders of peripheral arterial blood flow."[27] The Committee for Proprietary Medicinal Products (CPMP) of the European Community also called for severe restrictions on the indications for the drug in 1991, limiting its use to prophylaxis of severe refractory migraine, and functional vestibular vertigo. "All other indications should be withdrawn," said the CPMP. Even with these indication, the CPMP pointed out that there was still a

Table 6B-1
Complaints made by the Medical Lobby for Appropriate Marketing (MaLAM) about promotion of brain tonics (1986-1991)

Company, Brand and generic names	Claims/indications
Abbott, Loftyl, buflomedil	"improved memory and concentration, improved reasoning ability, better sleep, improved adaptation to environment", Pakistan, late 1988[1]
Bayer, Nimotop, nimodipine	"FDA approved", "changes in brain function... such as reduced capacity for concentration and memory, depression, fear, lack of initiative, lack of social contact, dizziness", Panama, Nov 1991[2]
Carlo Erba, Sermion, nicergoline	"symptoms of chronic cerebral insufficiency", Indonesia June 1988; "chronic cerebral insufficiency, senile and pre-senile dementia", Philippines, April 1988[3]
Hoechst, Trental, oxpentifylline	"prevent recurrent ischaemic attacks... improve cognitive and mental function", Indonesia, 1990[4]
Janssen, Sibelium, flunarizine	"lack of concentration, confusion, memory disorder, irritability", "safe", Hong Kong, December 1986[5]
Roussel, Targifor, arginine aspartate	"comprehensive treatment for fatigue and stress... for... the elderly... increases concentration... increases intellectual output", Uruguay, 1991[6]
Sandoz, Hydergine, co-dergocrine	"impressive improvement of the symptoms of cerebral insufficiency", Pakistan, 1986; "symptoms of mental decline (confusion, dizziness, memory lapses)", Philippines, 1986[7]

Sources: Letters from MaLAM to the companies – 1) to Abbott, Jul 1989; 2) to Bayer, Sep 1992; 3) to Farmitalia Carlo Erba, Aug 1988; 4) to Hoechst, Nov 1990, 5) to Janssen, Sep 1987; 6) to Roussel, Mar 1991; 7) to Sandoz, Feb 1987

need for extensive, double-blind clinical studies "in order to support the benefit/risk ratio" of the drug. The CPMP also proposed that product information should contain a "special warning" pointing out that use of the drug "may give rise to extrapyramidal and depressive symptoms and reveal Parkinsonism, especially in predisposed patients such as the elderly. Therefore, it should be used with caution in such patients."[28]

Ergoloid mesylates

Ergoloid mesylates such as Deapril-ST, Hydergine, and Gerimal have been reported to produce modest improvement of confusion, depressed mood, dizziness, unsociability, and self-care in controlled clinical trials. The AMA notes however, that "it is difficult to predict which patients will benefit".[29] That did not stop Sandoz from achieving global sales of $227.6 million for Hydergine in 1987.[30]

Goodman and Gilman point out that "the mixture of ergoloid mesylates has been widely employed in the treatment of senile dementia. In a few apparently well-controlled studies, patients... have displayed slight improvement in some behavioural or other psychological measures.... The mechanisms that underlie any beneficial responses are poorly understood, and the subject remains controversial."[31]

In the UK, the BNF notes that "some improvements in performance of psychological tests have been reported but the drugs have not been shown clinically to be of much benefit in senile dementia."[32] *Martindale* reports on various trials but makes the point that although improvements could be found on some behavioural or psychological measures, conclusions as to the therapeutic usefulness of co-dergocrine mesylate were "guarded".[33]

In the United States, the FDA requires Sandoz to include the following information in its labelling and product information:

> "... nor is there conclusive evidence that the drug particularly affects cerebral arteriosclerosis or cerebrovascular insufficiency. *Indications*: A proportion of individuals over 60 who manifest signs and symptoms of an idiopathic decline in mental capacity... can experience some symptomatic relief upon treatment with Hydergine.... The identity of the specific trait(s) or condition(s), if any, which would usefully predict a response to Hydergine therapy is not known.... The decision to use Hydergine in the treatment of an individual with a symptomatic decline in mental capacity of unknown etiology should be continually reviewed since the presenting clinical picture may subsequently evolve sufficiently to allow a specific diagnosis and a specific alternative treatment.... *Precautions*: Practitioners are advised that because the target symptoms are of unknown etiology, careful diagnosis should be attempted before prescribing Hydergine preparations."[34]

In 1990, a study published in the *New England Journal of Medicine* concluded that Hydergine was "ineffective as a treatment for Alzheimer's disease".[35] This prompted the Public Citizen group in the USA to call on the FDA to ban ergoloid mesylates. Public Citizen said that the new study served to demonstrate the poor quality of earlier research.[36]

A poor research record

According to the *Drug and Therapeutics Bulletin*, none of the drugs being promoted in the UK for related conditions, such as intermittent claudication (limping caused by an inadequate supply of blood to the muscles), are worth using. However, they cost the National Health Service more than £25 million (US$ 37.5 million) a year. The products that were evaluated were: inositol nicotinate (Hexopal by Winthrop), naftidrofuryl (Praxilene by Lipha), oxpentifylline (Trental by Hoechst), cyclandelate (Cyclospasmol by Brocades), nicofuranose (Bradilan by Napp), cinnarizine (Sturgeon Forte by Janssen), nicotinyl alcohol (Ronicol by Roche).[37] One of those products, Hoechst's Trental (oxpentifylline) had global sales of $380 million in 1990,[38] with 1993 sales estimated by Nikko Securities to be $446 million.[39] In 1991, the Swedish drug regulatory authority, after 10 years of studying the drug, rejected an application for a product licence for Trental on the grounds that the quality of the clinical studies was poor.[40]

One industry analyst says that "the pharmaceutical industry has an abysmal record in treating disorders of the brain and nervous system.... For the most serious problems – degenerative brain diseases such as Alzheimer's – there is still nothing that really works."[41] This is confirmed by the *Drug and Therapeutics Bulletin* which said in 1991 that "drugs now available for treating Alzheimer's disease offer no clinically significant benefit".[42]

The fear of Alzheimer's disease, which causes about half of all cases of senile dementia,[43] has triggered off a wave of research. Among the products to emerge is tacrine, manufactured by Warner-Lambert as Cognex. An early study that raised hopes was subsequently questioned and led the US FDA to call for further evidence of efficacy and safety. The FDA was particularly concerned about the possibility that tacrine could cause liver damage. In 1991, the FDA granted an investigational licence for the drug, but asked for further efficacy studies before full approval could be given.[44] Initial results show some improvements in some patients. However, this research suggests that tacrine "is not for everyone".[45] A similar drug, velnacrine maleate (produced by Hoechst-Roussel as Mentane) has been found by an FDA advisory committee to have an unacceptable

risk-benefit ratio. The committee was particularly concerned about the risk of agranulocytosis that had appeared in the early studies.[46]

Age-associated memory impairment

The difficulty in identifying a suitable therapy for Alzheimer's is perhaps one of the reasons for the recent emergence of a syndrome called age associated memory impairment (AAMI). The starting point for the syndrome is "benign forgetfulness" which are mild memory impairments that usually do not deteriorate. By the mid-1980s, a definition of the syndrome began to emerge that mirrored in some ways the early definition of MBD in children. The definition was so broad that most people over 50 could probably be included, in the same way that most children could have been included in the MBD definition. One of the factors that makes the definition so all-inclusive is that it compares the memory power of a healthy non-demented adult over 50 to that of a young adult. It is almost inevitable that memory performance will be worse in older people. An editorial in the *British Medical Journal* says that the syndrome is "too broad an entity to justify drug treatment yet".[47]

Clearly, however, the pharmaceutical industry is interested in having the aging process defined as a disease so that, in the words of Prof. James McGaugh of the Center for Neurobiology of Learning and Memory at the University of California, Irvine, "something that normally occurs now will be called a disease, so it can then be treated by a drug to improve memory". Prof. Ian Hindmarch calls AAMI "a pseudo-disease. It's having a drug and wanting an illness for that drug. It's a modern disease, when pharmaceutical chemists can produce hundreds of molecules and the industry is desperately wanting to get these molecules on the market."[48]

Sandoz is one of the companies hoping to cash in on AAMI. It has produced a booklet promoting Hydergine called *Age-Related Mental Decline and Dementias: The Place of Hydergine*.[49] The Belgian company UCB is also hopeful. Its brand of piracetam, Nootropil, was advertised in the Middle East in December 1990 as a product for "memory, concentration" which "activates, protects and restores metabolism, circulation and functions of the brain cortex".[50] With global sales of $100.7 million for the product in 1990, the company is looking for new markets.[51] The product was licensed in the UK in early 1993 for the treatment of cortical myoclonus, a condition that results from brain damage and affects only about 50-60 people in the UK. However, the company hopes that additional indications will be approved in the future. The company says it is not seeking the indication of AAMI for the product in the UK "as current data would probably not be sufficient for the UK authorities, which are believed to take a stricter view of this condition than many other regulatory

"Are your neurons tired? You'll feel better with Cogitum" - a 'psychostimulant' for French pharmacists, in Le Quotidien du Pharmacien, 20 Jan 1992

agencies." However, UCB recognises that there may well be some "off label" use of Nootropil for AAMI.[52]

Glaxo is a company which has clearly targeted AAMI. It says early trials of ondansetron (produced as Zofran and registered in the UK to treat nausea caused by cancer chemotherapy) provide evidence that it is the "first pharmaceutical agent that has been effective in normalising a memory impairment".[53] Glaxo's director of clinical research on the central nervous system, Dr Paul Williams, says that the company believes that "at least four million people in the United Kingdom suffer from age-associated memory impairment, so if it is eventually made available to them, there'd be an awful lot of people very interested indeed".[54]

"Smart" drugs

There are another group of people who are interested in drugs that might improve memory. The idea appeals to students everywhere and increasingly has been taken up by business people who want to be able to compete more effectively. Some people in the USA are spending as much as $600 a month[55] consuming a cocktail of "cognitive enhancers", vitamins and nootropics – collectively called "smart drugs" – in the hope that the drugs will increase their brain power, improve their memory, their concentration and their ability to learn.

Those supposed effects reflect the often unfounded claims that have been made for these products in promotional advertising over the years. While the evidence is sparse to suggest that these products are effective in disease conditions, there is absolutely no evidence to support their efficacy among healthy people. Professor Steven Rose, of the Brain and Behaviour Research Group at the Open University in the UK, says that "if a normal person takes drugs which are developed for this purpose, then the best that you could have is what one might call the placebo effect – that is, that people would expect to feel better as a result of taking them, and then maybe they would."[56]

Prof. Hindmarch describes the appeal of "smart" drugs as being "very compelling". He says that, "if you believe that these drugs enhance your concentration and memory", there is a tendency "for you to take them for life, and of course, this is why there are many pharmaceutical companies who would wish you to start taking them. If you can perform better in your school by using drug X, then this means you've probably got to take drug X for the rest of your life."[57]

The drawback – other than the lack of efficacy – is the risk of side effects. This is already a high risk with some of these products; using them in an unsupervised way simply increases the risk. The US FDA is concerned about this and is trying to crack down on the selling of these products as "smart" drugs.[58] As Prof. Rose points out, "it can be harmful to throw chemical spanners into the workings of the human brain".[59]

[See also the sections on *Vitamins*, *Growth Stimulants*, *Children and Drugs*, and *Drugs and the Elderly*.]

Recommendations for action

Because there is very little good evidence to justify the efficacy of most of the products used for mental and behavioural disorders, because many of them are likely to cause serious side effects, and because they are generally expensive and unnecessarily divert scarce resources, their sale and promotion need to be subject to stricter controls.

1. Governments should review the products currently on the market for the treatment of cerebral dysfunction in the elderly, and products for learning and behavioural disorders in children, with a view to removing ineffective preparations and introducing much stricter controls on the indications, claims, and prescribing information allowed for any products that remain on the market.

2. The use of amphetamines and amphetamine-like drugs in the treatment of learning and behavioural disorders in children should be severely restricted. These products should be removed from the *regular* market and be permitted for use only by specialists when there is clear evidence of a measurable brain disorder.

3. Strict controls should be introduced to prevent the non-medical use of psychoactive drugs in the false hope that memory, concentration or intelligence can be improved.

4. Independent information about the treatment of senile dementia and of behavioural and learning disorders in children should be prepared for health workers to remove the dependence on misleading promotional material prepared by the industry. There should be greater emphasis on non-drug solutions to these problems, such as counselling and memory training.

References:

1. MaLAM, letter to Roussel, Mar 1991; Anon., "MaLAM questions Roussel on arginine aspartate", *Scrip*, No 1609, 19 Apr 1991, p13
2. Clayton, P., "Can a pill make you more intelligent?", *Evening Standard* (London), 24 Jul 1991
3. BBC, *Food for Thought* (Transcript of "Horizon" programme transmitted 10 Jun 1991), London, Broadcasting Support Services, 1991, p21
4. Moran, J., *Alzheimer's Disease: New Therapies and the World Market*, London, Financial Times Management Reports, 1991
5. Melville, A. and Johnson, C., *Cured to Death*, London, New English Library, 1982, pp72-4
6. Braithwaite, J., *Corporate Crime in the Pharmaceutical Industry*, London, Routledge & Kegan Paul, 1984, p222
7. Melville and Johnson, op cit, pp72-4
8. AMA, *Drug Evaluations*, Philadelphia, W.B. Saunders Co., (6th edn) 1986, p162
9. Brown, C.S., "Treatment of attention deficit hyperactivity disorder: a critical review", *DICP, The Annals of Pharmacotherapy*, Vol 25, Nov 1991, pp1207-13
10. AMA, op cit, p163
11. Hechtman, L., "Resilience and vulnerability in long term outcome of attention deficit hyperactive disorder", *Canadian Journal of Psychiatry*, Vol 36, No 6, Aug 1991, pp415-21
12. Everett, J., Thomas, J., et al, "Cognitive effects of psychostimulant medication in hyperactive children", *Child Psychiatry and Human Development*, Vol 22, No 2, Winter 1991, pp79-87
13. Rosenberger, P.B., "Attention deficit", *Pediatric Neurology*, Vol 7, No 6, 1991, pp397-405
14. Rylance, G. (ed.), *Drugs for children*, Copenhagen, WHO, 1987, p89
15. E. Merck, *Encephabol Prospectus*, Darmstadt (Germany), Jan 1986 (English translation of the German original for the company by J. T. Lazandes)
16. Rylance, op cit, p89
17. MaLAM, letter to E. Merck, Apr 1988
18. Hosking, G., "Drug marketing in the Third World", *Lancet*, 1986 (Vol II), p164
19. Silverman, M., Lydecker, M. and Lee, P.R., *Bad Medicine: the prescription drug industry in the Third World*, Stanford, Stanford University Press, 1992, pp35-6, 298-9
20. Parish, P., *Medicines: a guide for everybody*, London, Penguin (6th edn, revised), 1989, p174
21. Gilman, A.G., Rall, T.W., Nies, A.S., and Taylor, P., *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, New York, Pergamon Press, (8th edn) 1990, p781
22. BMA and the Royal Pharmaceutical Society of Great Britain, *British National Formulary*, London, BMA and The Pharmaceutical Press, No 23, Mar 1992, p92
23. Birley, J.L.T., "Drug advertising in developing countries", *Lancet*, 28 Jan 1989, p220
24. Mansfield, P.R., "Classifying improvements to drug marketing and justifications for claims of efficacy", *International Journal of Risk & Safety in Medicine*, Vol 2, 1991, pp171-84
25. Silverman, et al, pp33-6 and 289-99
26. *MaLAM Newsletter*, Aug 1987
27. Anon., "Germans restrict flunarizine use", *Scrip*, No 1599, 15 Mar 1991, p23
28. Anon., "CPMP restricts flunarizine indications", *Scrip*, No 1601, 22 Mar 1991, p22
29. AMA, op cit, p162
30. Anon., "Monitor: R&D And Expansion To Boost Sandoz", *IMS Marketletter*, 14 Nov 1988 (according to Mark Edmiston and Kah Foo of SBCI Savory Milln)
31. Gilman, et al, p946
32. BMA and the Royal Pharmaceutical Society of Great Britain, op cit, p92
33. Reynolds, I.E.F. (ed.), *Martindale: The Extra Pharmacopoeia*, London, The Pharmaceutical Press, (29th edn) 1989, p1051
34. *Physicians' Desk Reference*, Oradell, NJ, Medical Economics Company, 44th edn, 1990, p1939
35. Thompson, T.L., Filley, C.M., et al, "Lack of efficacy of Hydergine in patients with Alzheimer's disease", *New England Journal of Medicine*, Vol 323, No 7, 16 Aug 1990, pp445-8
36. Anon., "Ergoloid mesylates ban urged in US", *Scrip*, No 1592, 20 Feb 1991, p23
37. Anon., "Present drugs fail in claudication", *Scrip*, No 1487, 9 Feb 1990, p27
38. Anon., "Top 50 branded products worldwide", *Scrip*, Review issue 1990, p21 (based on Barclay de Zoete Wedd's "Pharmaceutical Industry Perspectives")
39. Anon., "Hoechst's 1989 pharma sales up 13.6%", *Scrip*, No 1516, 23 May 1990, p11
40. Anon., "Swedes reject pentoxifylline", *Scrip*, No 1601, 22 Mar 1991, p21
41. Cookson, C., "New era looks to mind drugs", *Financial Times*, 26 Jun 1992, p12
42. Anon., "Economic prescribing", *Drug and Therapeutics Bulletin*, Vol 29, No 2, 21 Jan 1991, p5
43. Anon., "Alzheimer's: the path of forgotten memories", *Health Horizons*, No 13, May 1991, pp26-8
44. Anon., "FDA panel urges further efficacy studies for Cognex", *Scrip*, No 1636, 24 Jul 1991, pp24-5
45. Anon., "Tacrine's benefits confirmed", *Scrip*, No 1770, 13 Nov 1992, p29
46. Anon., "Mentane risk-benefit unacceptable", *Scrip*, No 1769, 10 Nov 1992, pp22-3
47. O'Brien, J.T. and Levy, R., "Age associated memory impairment", *British Medical Journal*, Vol 304, 4 Jan 1992, pp5-6
48. BBC, op cit, pp20 and 22
49. Cited in: Dean, W. and Morgenthaler, J., *Smart Drugs and Nutrients*, Santa Cruz, Calif., B&J Publications, 1990, p15
50. *MIMS Middle East*, Dec 1990, p67
51. Anon., "Piracetam leads UCB's pharma sales", *Scrip*, No 1650, 11 Sep 1991, p14
52. Anon., "Piracetam approved in the UK", *Scrip*, No 1797, 23 Feb 1993, p21
53. Anon., "Ondansetron in psychiatry - cautious optimism", *Scrip*, No 1626, 19 Jun 1991, pp24-5
54. BBC, op cit, p22
55. Anon., "Nootropics: steroids for stockbrokers?", *Scrip*, No 1626, 19 Jun 1991, p26
56. BBC, op cit, p9
57. Ibid, pp24-5
58. Anon., "FDA cracks down on 'smart drugs'", *Scrip*, No 1713, 29 Apr 1992, p16
59. Anon., "Smart Drugs", *Which? Way to Health*, Feb 1993, pp22-5

Chetley, A. *Problem Drugs*, Amsterdam,
Health Action International, 1993

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6C. Vitamins

Vitamins stimulate growth...

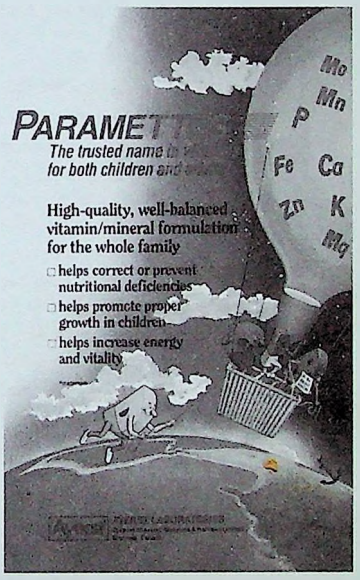
of the pharmaceutical industry

Vitamins are organic compounds which are necessary for good health. Food is the best source of vitamins and minerals. Healthy persons eating an adequate balanced diet will not benefit from additional vitamins.[1]

Although malnutrition and disease in developing countries can contribute to quite severe vitamin deficiencies which can be corrected with large doses of specific vitamins, in the long term the answer lies in improving the diet. The widespread promotion of vitamins helps to "medicalise" hunger so that the economic and social causes of malnutrition are not tackled. Instead, the focus is placed on "cure" and treatment and scarce financial resources are spent on unnecessary vitamins rather than necessary foodstuffs.[2] (See the box about vitamin A supplements on the following page.)

Lack of a vitamin caused by an inadequate diet may lead to a specific deficiency syndrome. Deficiencies can also occur because of malabsorption of food or be due to an increased metabolic need, for example, during pregnancy or lactation. In these circumstances, it is *sometimes* useful to include vitamin supplements as a part of the therapy. However, according to the American Medical Association (AMA), "there are few valid indications for vitamin or mineral supplements.... Massive-dose therapy usually is justified only in patients who cannot utilize nutrients properly, in those with certain diseases, or in those with inborn errors of metabolism".[3]

In industrialised countries, clearly identifiable vitamin deficiencies are rare, except in some specific sub-groups of the population. In the UK, for example, the British Medical Association (BMA) says that most people "obtain sufficient quantities of vitamins in their diet, and it is therefore unnecessary in most cases to take



Dubious claims for multivitamins "for the whole family", in Mims Caribbean, Jan 1990

The 13 vitamins

Water soluble	Fat soluble
ascorbic acid (vitamin C)	vitamin A
thiamine (B1)	vitamin D
riboflavine (B2)	vitamin E*
nicotinic acid or niacin (B3)	vitamin K
pyridoxine (B6)	
cobalamin (B12)	
folic acid	
biotin*	
pantothenic acid*	

*therapeutic value not proven and natural deficiency is extremely rare

additional vitamins in the form of supplements".[4] In the USA, "clinically apparent vitamin deficiencies are rare... and subclinical deficiencies are difficult to detect".[5] As a result, the American Institute of Nutrition, the American Society for Clinical Nutrition, the American Dietetic Association and the National Council Against Health Fraud, together with the AMA's Council on Scientific Affairs issued a statement pointing out that:

> "Healthy children and adults should obtain adequate nutrient intakes from dietary sources. Meeting nutrient needs by choosing a variety of foods in moderation, rather than

Vitamin A supplements

An estimated 40 million children worldwide under five years of age suffer from vitamin A deficiency. As a result, about 400,000 die and more than 250,000 children a year become partially or completely blind.[1] Vitamin A deficiency increases the severity and the risk of the three main health threats facing children in developing countries: diarrhoeal diseases, measles and pneumonia. The pooled evidence from six separate investigations in India, Indonesia and Nepal over the past 10 years indicates that child deaths can be reduced by about one-third by improving children's vitamin A intake.[2]

In these six investigations, the improvements have come about after giving a high dose (200,000 international units – IU) of vitamin A every six months or, in the case of one of the Indian studies, weekly doses of 8,333 IU of vitamin A. This Indian study found a reduction in childhood mortality of 54%,[3] but the other Indian study concluded that vitamin A supplementation alone might not reduce child mortality.[4] That was also the conclusion of a study carried out in northern Sudan.[5] The authors said that "reducing poverty, improvements in sanitation, and access to adequate diets should remain the main goals to improve child survival".

This is the crux of an important debate and one which affects attitudes towards vitamins in general as well as the rational use of other drugs. In the words of the Indian researcher, C. Gopalan, "there are just no miracle drugs, magic bullets and short-cuts in the war against poverty and malnutrition".[6] He argues strongly that vitamin supplements are not the solution to deficiencies.

> "The logical way to ensure vitamin A nutrition is through dietary improvement, and fortunately the countries afflicted with vitamin A deficiency have an abundance of natural food resources to combat it. These countries must be helped to harness their food resources for this purpose; and they should not be misled, through exaggerated claims, into relying perpetually on periodic medication with massive doses of synthetic vitamin A – an approach that was initially adopted purely as a short-term measure."

Other researchers are also calling for caution in the rush to provide vitamin A supplements. A third Indian study concluded that vitamin A alone was not enough "to solve the problems of health and nutrition". It called for social and public health programmes to work on literacy, education, employment, immunisation and sanitation as well as "the promotion of child feeding initiatives based on locally available, affordable, culturally acceptable, nutritious foods, including those high in vitamin A".[7]

The main point that critics of the supplementation route make is that this type of intervention cuts across all the social and political goals of primary health care. As Anthony Costello of the Institute of Child Health in London points out, vitamin A supplements should be widely available as one of the tools for primary health care, "but international agencies should think carefully before supporting vertically run national vitamin A supplementation programmes. Money might be spent more effectively and sustainably on initiatives to improve an integrated primary health care service through better management and training, and the development of an organisational culture which makes these services more user-friendly for poor and disadvantaged families, one of whose problems is vitamin A deficiency."[8]

As an editorial in *The Lancet* in 1990 concluded, the evidence seems clear that dealing with vitamin A deficiency will have public health benefits beyond the immediate deficiency problems. The challenge, however, is to identify how to improve vitamin A intake in ways "that are effective and sustainable at a community level".[3]

Sources:
1. Ramalingaswami, V., "Challenges and opportunities – one vitamin, two minerals", *World Health Forum*, Vol 13, No 2/3, 1992, pp222-31
2. UNICEF, *The State of the World's Children 1993*, Oxford and New York, Oxford University Press, 1992, p12
3. Anon., "Vitamin A and malnutrition/infection complex in developing countries", *Lancet*, Vol 336, 1 Dec 1990, pp1349-50
4. Vijayaraghavan, K., Radhaiah, G., et al, "Effect of massive dose vitamin A on morbidity and mortality in Indian children", *Lancet*, Vol 336, 1 Dec 1990, pp1342-5
5. Guillermo Herrera, M., Nestel, P., et al, "Vitamin A supplementation and child survival", *Lancet*, Vol 340, 1 Aug 1992, pp267-71
6. Gopalan, C., "Vitamin A deficiency and childhood mortality", *Lancet*, Vol 340, 18 July 1992, pp177-8
7. Ranmathullah, L., Underwood, B.A., et al, "Diarrhea, respiratory infections, and growth are not affected by a weekly low-dose vitamin A supplement: a masked, controlled field trial in children in southern India", *American Journal of Clinical Nutrition*, Vol 54, 1991, pp568-77
8. Costello, A.M.de L., "Vitamin A supplementation", *Lancet*, Vol 338, 31 Aug 1991, p568

The *BNF* also advises that there is "little place for the use of vitamin B12 orally" and "there is *no* justification for prescribing multiple-ingredient vitamin preparations containing vitamin B12 or folic acid".[39]

Selling a cure for tiredness...

The French company, Servier, promoted Arcalion 200 (vitamin B1 - sulbutiamine) in the Middle East in 1990, and in Africa and the Caribbean in 1991 as a treatment for "all forms of functional asthenia [weakness or fatigue]", and recommends taking two of the 200mg tablets "with breakfast" every day.[40] The recommended daily allowance for vitamin B1 is 1.5mg for an adult.[41] The healthy human body contains only about 25mg of the vitamin. Furthermore, it has no means of storing any excess taken in the diet. This product has the general properties of thiamine[42] and "there is no evidence that thiamine is of value for anything other than deficiency".[43] A computer search carried out by the Medical Lobby for Appropriate Marketing (MaLAM) of the medical literature of the past 15 years was only able to turn up one article on the use of sulbutiamine; however, it was of such poor quality that it could not be used to demonstrate proof of efficacy of the product.[44]

... a cure for infertility...

In April 1991, SmithKline Beecham advertised its multivitamin with zinc preparation, Zevit, in the Indian edition of the *Journal of the American Medical Association* for a long list of indications that included: "... mood alteration, loss of libido, infertility, impotence, lethargy, depression". Once again, MaLAM searched the literature: this time it was unable to find any controlled trials of Zevit or an equivalent combination that provided any evidence for the indications.[45]

...a way to promote children's growth...

In the Caribbean in 1991, Abbott advertised its multivitamin and mineral preparation, Parametres, as a product that "helps promote proper growth in children, helps increase energy and vitality". Children need food to grow properly and to have sufficient energy and vitality. Promoting vitamins as growth stimulants is a practice that is both misleading and unethical.

... a way to promote children's intelligence...

In 1992, in the UK, three vitamin manufacturers – Seven Seas (Boost IQ), Raw Power (Vitachieve), and Larkhall Laboratories (Tandem IQ) – were all successfully prosecuted for claiming that their vitamin products could increase children's intelligence.[46] Once again, the evidence to support the claims was lacking (see the box about vitamins and intelligence on the previous page).

... a tonic to fight tiredness and boost appetite

In 1993, in a leaflet available to the public in pharmacies in the UK, Pharmax promoted its Effico Tonic as the "pick-me-up" to "build up your appetite, restore your vitality, and allow you to enjoy life to the full again". Primarily based on vitamins B1 and B3, it also contained a little caffeine ("fights tiredness") and some gentian bitter to "promote appetite".

Controlling the market

In most countries, the market is littered with ineffective products, with irrational combinations or formulations, or with high-dose vitamins posing an unnecessary threat to health and an additional financial burden. A survey of prescribing guides from five regions of the world in 1985 found that more than three-quarters of the 888 vitamin preparations listed could not be recommended.[47] The situation has not improved as Table 6C-1 shows. During 1990-91 of the 636 vitamins listed in prescribing guides in four regions of the world, more than four out of every five could not be recommended. In the USA, a 1991 report found that the amounts of vitamins in more than 3,400 different preparations on the market in 1986 varied enormously. They could include anything from 7% of the RDA of vitamin E to 50,000% of the RDA of vitamin B6 in single ingredient preparations, and less than 0.5% of the RDA of vitamins A, E, B1, B3, or B6 to as much as 53,333% of the

Table 6C-1
Vitamins on sale in selected markets (1990-1991)

Description	Pakistan		Middle East		Africa		Caribbean	
	No.	%	No.	%	No.	%	No.	%
Total no. of vitamins	263		195		94		84	
Indications:								
For therapeutic use	94	35.7	111	56.9	60	63.8	58	69.1
Prophylaxis/supplement	172	65.4	85	43.6	33	35.1	23	27.4
Unproven indications	109	41.4	140	71.8	67	71.3	62	73.8
Formulation:								
Non-essential ingredient	96	36.5	99	50.8	41	43.6	34	40.5
Irrational formulation	122	46.4	125	64.1	55	58.5	54	64.3
Excessive dosage	120	45.6	95	48.7	39	41.5	32	38.1
Not Recommended	204	77.6	175	89.7	84	89.4	70	83.3

Total vitamins all areas: 636
Total not recommended: 533 (83.8%)

Sources: *QIMP* (Pakistan), Mar-Aug 1990; *MIMS Middle East*, Dec 1990, p128; *MIMS Africa*, Jul 1991, p98; *MIMS Caribbean*, Jan 1991

have no beneficial effect in patients with advanced cancer". It also says that megadoses of vitamin C have not been found to have any effect on atherosclerosis, healing of wounds or schizophrenia and that there are a variety of diseases – including asthma and male infertility – for which there is not enough evidence to conclude whether vitamin C is of any use.[28]

There is no evidence to support the efficacy of vitamin E in the numerous conditions for which it is popularly used. "Large doses do not protect against arteriosclerosis, cancer, pulmonary damage from air pollution, or deterioration from aging, and vitamin E is ineffective in inflammatory skin disorders, habitual abortion, heart disease, menopausal syndrome, infertility, peptic ulcer, burns, and porphyria."[29]

If doses of the vitamins on their own are ineffective for such ailments, there is little likelihood that if they are all combined together their effectiveness will improve. However, many of the multivitamin "tonics" claim to do just that. According to the BMA, "vitamin supplements should not be used as a general tonic to improve well-being – they do not do so – nor should they be used as a substitute for a balanced diet".[30] A UK consumer guide to medicines makes the point that "multivitamin tablets are mainly of value to the manufacturers".[31]

Professor Peter Parish notes that manufacturers give the impression that the recommended daily allowances of vitamins and minerals are to be *added* to a normal diet. He advises: "do not be misled: vitamins may be required to supplement an inadequate diet but never to complement a diet. High-dose vitamin preparations should be avoided – do not be attracted because they are called 'super vitamins' or any other name that indicates that the dose is above what is normally required."[32]

Even for conditions where vitamin supplementation is *sometimes* useful, not every patient will require them. Usually it is assumed that *all* women who are pregnant or lactating, infants and growing children, and the elderly *require* vitamin pills. However, for pregnant women, "a balanced diet is a better basis for health than vitamin supplementation";[33] for children, vitamins are only recommended in the rare cases of specific deficiency states, when inadequate diet occurs as a result of cultural traditions, or when children have specific metabolic disorders or experience malabsorption;[34] and for the elderly, "the most important step that you can take to maintain your nutritional well-being is to eat a healthy and well-balanced diet".[35]

Ineffective ingredients

Some vitamin preparations, in addition to being promoted for the wrong use, contain ingredients that are unnecessary or useless. The AMA advises that in multivitamin preparations, "additional components, such as liver, yeast, and wheat germ, do not confer any special advantage over the pure chemical ingredients, and inclusion of agents that have no proved value (eg. choline, methionine, lecithin, bioflavonoids, inositol) is unwarranted".[36] The *British National Formulary (BNF)* says that "there is no evidence" of the value of ingredients such as pantothenic acid, biotin, choline, or inositol.[37] *Martindale* says that pantothenic acid "has no accepted therapeutic use"; biotin has "no clearly defined therapeutic uses"; "a deficiency syndrome has not been identified in man and daily requirements have not been established" for choline and "its functions do not justify its classification as a vitamin"; and inositol "has an uncertain status as a vitamin and a deficiency syndrome has not been identified".[38]

Vitamins and intelligence

Claims that vitamins can boost intelligence have been around almost as long as vitamins. The roots of the claims lie in the widely accepted evidence that malnutrition can affect brain development and mental functioning. Thus, a deficiency in vitamins could also be linked to poor mental performance. The subsequent leap in faith, however, that increasing the intake of vitamins in otherwise well nourished individuals would increase their intelligence, is unproven.

Not that there haven't been attempts. A 1988 study carried out in Wales claimed that vitamin supplements improved children's non-verbal intelligence.[1] It was followed up by another study in 1988 that found no improvement in intellectual performance among children in London given vitamin supplements,[2] and a study in Scotland in 1990 that found no improvement on reasoning tests by children taking vitamin and mineral supplements.[3] A Belgian study in 1990 suggested that there might be a sub-set of children who consume a poor diet who could benefit from vitamin and mineral supplementation.[4] A study among schoolchildren in California, published in 1991 once again suggested that there might be some benefit from supplementation; however, the results were uneven within each sample group and it was a short-term trial. *The Lancet* concluded that "the case for vitamin and mineral supplementation as a method of increasing a child's IQ remains unproven".[5]

Sources:
1. Benton, D. and Roberts, G., "Effect of vitamin and mineral supplementation on intelligence of a sample of schoolchildren", *Lancet*, 23 Jan 1988, pp140-3
2. Naismith, D.J., Nelson, M., et al, "Can children's intelligence be increased by vitamin and mineral supplementation?", *Lancet*, 6 Aug 1988, p335
3. Crombie, I.K., Todman, J., et al, "Effect of vitamin and mineral supplementation on verbal and non-verbal reasoning of schoolchildren", *Lancet*, Vol 335, 31 Mar 1990, pp744-7
4. Benton, D. and Buts, J-P., "Vitamin/mineral supplementation and intelligence", *Lancet*, Vol 335, 12 May 1990, pp1158-60
5. Anon., "Brains and vitamins", *Lancet*, Vol 337, 9 Mar 1991, pp587-8

by supplementation, reduces the potential risk for both nutrient deficiencies and nutrient excesses."[6]

A growing market

Vitamins provide a profitable market for the pharmaceutical industry. A study of vitamin use among the elderly in 12 European countries found that much of the time the use of vitamin supplements does not correspond to nutritional needs.[7] In 1988, sales of vitamin and mineral supplements in the UK were estimated at £108 million (US $194 million).[8] In 1991, Germans spent nearly $348 million on over the counter (non-prescription) vitamin and mineral preparations.[9] In the USA, a 1987 survey (reported in 1990) found that more than 51% of all adults had taken a vitamin/mineral supplement within the previous 12 months, and 23% did so daily.[10] Women were more likely to use vitamins than men.[11] The US market for over the counter vitamins and mineral preparations was worth more than $2 billion in 1984;[12] estimates predicated sales of more than $3.5 billion a year by 1990.[13]

Adverse effects

Although it is generally believed that vitamins are harmless, there are real dangers related to the use of some of them. "Excessive use of one or more vitamins may cause relative deficiencies of other essential micronutrients, and large doses of all minerals, fat-soluble vitamins, and some water-soluble vitamins are toxic."[14]

Large amounts of vitamin A, which is fat-soluble, can produce loss of appetite, itching, skin disorders, loss of weight, enlargement of the liver and spleen, debility and painful swellings of bone and joints.[15] High doses of vitamin A given to pregnant animals have caused deformities,[16] and evidence of a teratogenic effect in humans[17] has led to recommendations that the recommended daily allowance (RDA) should not be exceeded during pregnancy. In the UK, pregnant women are advised that they should take care not only with vitamin A supplements, but also refrain from consuming large dietary amounts of vitamin A from food such as liver.

Excessive doses of vitamin D produce a rise in blood calcium which causes debility, drowsiness, nausea, abdominal pains, thirst, constipation, loss of appetite, deposits of calcium in various tissues and organs, kidney damage and kidney stones.[18] The AMA advises that "vitamin D supplements should be avoided in individuals, especially infants and children, who have adequate exposure to sunlight or a normal diet".[19]

Prolonged overconsumption of vitamin D in infants can cause mental and physical retardation, kidney failure and death. Symptoms of toxicity may occur with doses greater than 25 micrograms (1,000 IU) daily. In children and normal adults, amounts exceeding 1.25 milligrams (50,000 IU), produce abnormally high concentrations of calcium in the blood, and prolonged use of massive doses ultimately results in irreversible kidney failure and death. If vitamin D is contained in any multivitamin preparation, the amount should not exceed the RDA of 10 micrograms or 400 IU.[20]

Because Vitamin E is also fat-soluble, large doses "should be used cautiously". The long-term use of doses as low as 270 to 540mg daily has been reported to cause nausea, muscular weakness, fatigue, headache and blurred vision in some patients.[21] There is no good evidence for vitamin E deficiency or for the need for supplementation.

The water-soluble vitamins (the B vitamins, and vitamin C) readily pass out of the body when excessive amounts are taken, so adverse effects are minimised. Nonetheless, doses of vitamin C greater than one gram per day may cause diarrhoea by irritating the intestines. Large doses can also interfere with the results of common blood tests. As well, a dose of one gram per day can raise blood levels of ethinyl estradiol. If women using oral contraceptives containing ethinyl estradiol abruptly stop taking vitamin C, contraceptive failure can result.[22] Large doses of vitamin B6 have caused severe nerve damage.[23]

Two "B vitamins" that should be avoided are vitamin B15 and vitamin B17. The AMA says, "the toxic substances known as vitamin B15 (pangamic acid) and vitamin B17 (laetrile) are neither nutrients nor vitamins. Laetrile contains 6% cyanide by weight and has caused chronic cyanide poisoning and death. Pangamic acid or pangamate may be mutagenic. Neither substance has any established nutritional or other usefulness."[24]

Fact versus fiction

Vitamins are claimed to be of value in a wide variety of conditions such as arthritis, asthma, nephritis, rheumatic fever, schizophrenia, and vascular disorders. In the USA, an important reason for taking vitamin supplements is "the erroneous belief that such preparations provide extra energy and make one 'feel better'".[25]

A popular myth is that the B vitamins, in particular B6, are useful in treating nausea and vomiting in pregnancy and also premenstrual tension (PMT). However, "these possible therapeutic effects need confirmation in properly controlled clinical trials".[26]

Vitamin C is popularly believed to be the cure for the common cold and, more recently, has been suggested as a cure for cancer. "Claims that vitamin C ameliorates colds or promotes wound healing have not been proved."[27] The AMA says that "there is good evidence that pharmacological doses of ascorbic acid

RDA of vitamin B1 in multivitamin preparations.[48]

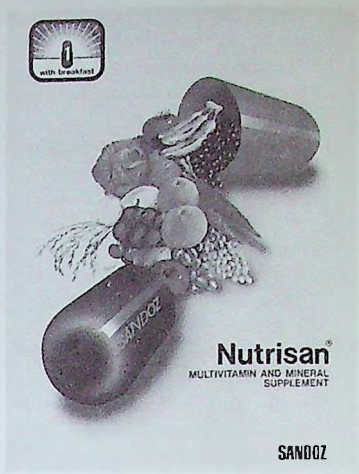
Misuse of vitamins can do harm. For example, it can:

- distort national health priorities;
- drain limited national economic resources and foreign exchange;
- waste limited individual and family financial resources;
- encourage incorrect and harmful beliefs about the nature of health; and
- encourage ineffective and harmful practices.

Access to good nutrition should be a priority for public health in all countries. Encouraging individual and government spending on unnecessary vitamin preparations does not contribute to public health needs. Rather, it reinforces the misleading belief that there is a magic pill that can fulfil those needs. The Sandoz Nutrisan advertisement from Pakistan in the late 1980s (pictured above) is an example of the type of pharmaceutical marketing that has contributed to that belief. By suggesting that the vitamin capsule can replace the nutrients in food, it diverts efforts to solve problems of hunger, malnutrition and vitamin imbalances.

[See also the sections on *Growth Stimulants*, *Brain Tonics*, and *Drugs in pregnancy*.]

Food in a capsule: Sandoz advertises Nutrisan in Pakistan



Recommendations for action

1. Governments should introduce strict controls over the claims made for vitamin preparations.
2. High-dose vitamins, used for treatment of specific deficiencies, should be clearly labelled and differentiated from preparations used as dietary supplements. If a deficiency does exist, single ingredient vitamins should be used rather than a multivitamin preparation.
3. Irrational vitamin combinations should be removed from the market.
4. Independent information about the rational use of vitamins should be developed for health workers and consumers.

References

1. AMA, *Drug Evaluations*, Philadelphia, W.B. Saunders Co., (6th edn) 1986, p841
2. Macdonald, J.J., *Primary Health Care: medicine in its place*, London, Earthscan, 1993, p25
3. AMA, op cit, p841
4. Henry, J. (ed.), *The British Medical Association Guide to Medicines & Drugs*, London, Dorling Kindersley, (2nd edn) 1991, p145
5. AMA, op cit, p859
6. Griffith, H.W., *The Vital Vitamin*, Wellingborough, UK, Thorsons, 1988, p1
7. Amorim Cruz, J.A., Moreiras-Varela, O., et al, "Intake of vitamins and minerals", *European Journal of Clinical Nutrition*, Vol 45 (Suppl. 3), 1991, pp121-38
8. Anon., "Who needs vitamin pills?", *Which?*, Feb 1990, p77
9. Anon., "Self-medication products in Germany", *Scrip*, No 1773, 24 Nov 1992, p4
10. Subar, A.F. and Block, G., "Use of vitamin and mineral supplements: demographics and amounts of nutrients consumed", *American Journal of Epidemiology*, Vol 132, No 6, 1990, pp1091-1101
11. Medeiros, D.M., Bock, M.A., et al, "Long-term supplement users and dosages among adult westerners", *Journal of the American Dietetic Association*, Vol 91, No 8, Aug 1991, pp980-2
12. Sanberg, P. and Krema, R.M.T., *Over-the-counter Drugs: Harmless or Hazardous?*, London, Burke Publishing, 1988, p81
13. *Chemical Market Review*, 8 Oct 1984
14. AMA, op cit, p859
15. Parish, P., *Medicines: a guide for everybody*, London, Penguin (6th edn, revised), 1989, p212
16. AMA, op cit, p847
17. Martinez-Frías, M.L. and Salvador, J., "Megadose vitamin A and teratogenicity", *Lancet*, 30 Jan 1988, p236; Anon., "Vitamin A intake in pregnancy", *Lancet*, Vol 336, 27 Oct 1990, p1063
18. Parish, op cit, p214
19. AMA, op cit, pp860-1
20. Ibid, pp848 and 860
21. Ibid, p849
22. Ibid, pp850-1
23. Grant, R., *Which? Medicine*, London, Consumers Association and Hodder & Stoughton, 1992, p466
24. AMA, op cit, p841
25. Gilman, A.G., Rall, T.W., Nies, A.S., and Taylor, P. (eds), *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, New York, Pergamon Press, (8th edn) 1990, p1528
26. Reynolds, J.E.F. (ed.), *Martindale: The Extra Pharmacopoeia*, London, The Pharmaceutical Press, (29th edn) 1989, p1271
27. BMA and the Royal Pharmaceutical Society of Great Britain, *British National Formulary*, London, BMA and The Pharmaceutical Press, No 23, Mar 1992, p341
28. AMA, op cit, pp850-1
29. Ibid, p849
30. Henry, op cit, p145
31. Cawson, R. and Spector, R., *Drugs and Medicines: a consumers' guide*, Oxford, Oxford University Press, 1990, p105
32. Parish, op cit, pp214-5
33. Phillips, A., Rakuser, J. (eds) and the Boston Women's Health Collective, *The New Our Bodies, Ourselves* (2nd UK edition), London, Penguin Books, 1989, p345
34. Rylance, G. (ed.), *Drugs for children*, Copenhagen, WHO, 1987, p147
35. Wolfe, S.M., Fugate, L., et al, *Worst Pills Best Pills*, Washington, Public Citizen Health Research Group, 1988, p426
36. AMA, op cit, p859
37. BMA and the Royal Pharmaceutical Society of Great Britain, op cit, p340
38. Reynolds, op cit, pp1257, 1258, 1266 and 1270
39. BMA and the Royal Pharmaceutical Society of Great Britain, op cit, p320
40. *MIMS Middle East*, Dec 1990, p128; *MIMS Africa*, jul 1991, p98; *MIMS Caribbean*, Jan 1991, p55
41. AMA, op cit, p844
42. Reynolds, op cit, p1276
43. AMA, op cit, p854
44. MaLAM letter to Servier, Apr 1990
45. MaLAM letter to SmithKline Beecham, Jan 1992
46. Anon., "UK vitamin manufacturer fined over IQ claims", *Scrip*, No 1763, 20 Oct 1992, p9
47. Chetley, A. and Gilbert, D., *Problem Drugs*, The Hague, HAI, 1986, p6 of Vitamins section
48. Park, Y.K., Kim, I, and Yetley, E.A., "Characteristics of vitamin and mineral supplement products in the United States", *American Journal of Clinical Nutrition*, Vol 54, 1991, pp750-9

Chetley, A. *Problem Drugs*, Amsterdam,
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Unnecessary risks

Margaret, aged 31, finally became pregnant in the USA after she and her husband had tried for years to have a baby. At about the same time, and before she realised that she was pregnant, a dermatologist started her on a treatment for cystic acne with a new drug, Accutane (isotretinoin). She took the drug for six weeks and her acne improved. At 34 weeks, Margaret had a premature delivery. Her baby girl weighed just over two kilograms, and was found to have water on the brain and defects in her heart. The baby, Susan, only survived for a few weeks.[1]

During the first three months (first trimester) of pregnancy, and particularly from the 18th to 60th day, while organs are developing, the fetus is most susceptible to drugs which may cause congenital malformations.[2] These teratogenic drugs may be lethal and lead to abortion, or to the birth of a child with defects. During the fourth to sixth month (second trimester) of pregnancy, teratogenic drugs can still cause disorders of growth and function, particularly in the brain and spinal cord, but these disorders are rarely fatal. Drugs given late in pregnancy may lead to problems during childbirth or immediately after, which may be fatal and are frequently related to drug-induced respiratory failure. This is particularly a problem in premature infants, whose lungs are poorly developed at birth.

Only an estimated 3% of congenital abnormalities are definitely due to drugs,[3] but the number of drugs that have been identified as causing abnormalities is growing. The best known is thalidomide. In November 1956, thalidomide was first marketed for use in a wide range of conditions including influenza, functional disorders of the stomach and gall bladder, mild depression, insomnia and menstrual tension. It was widely promoted, without sufficient evidence, as a safe and effective drug to be used during pregnancy. The resulting tragedy of some 10,000 severely deformed babies is now history.[4]

Over the years, the list of teratogenic drugs has grown to include thalidomide, anti-cancer drugs, hormones (including DES), warfarin, penicillamine, antithyroids, anticonvulsants, inhalation anaesthetics, alcohol, some psychotropic drugs, tetracycline and other antibiotics, and retinol derivatives.[5] A teratogenic effect could exist for high doses of vitamin A.[6] Table 7A-1, on the next page, describes the system devised by the Australian Drug Evaluation Committee to classify the risk of various drugs in pregnancy.

The use of drugs in pregnancy continues to be a controversial, little known area, both in terms of risks and benefits. There are very few drugs that are certainly safe in early pregnancy. One leading textbook on pharmacology points out that "the fetus is to at least some extent exposed to essentially all drugs taken by the mother".[7] If drugs are necessary during pregnancy or when pregnancy is a possibility, those which have been extensively used and shown to be usually safe are to be preferred to new drugs.

Overuse

The thalidomide tragedy had a profound effect on attitudes toward drug safety and in particular to prescribing or using medicines during pregnancy. However, both too many and too wide a range of drugs are still being used in pregnancy.

A 22-country study carried out in the late 1980s, which included women from Europe, Asia, Latin America, and Africa, found that only 14% of women did not take any drugs during their pregnancy. Among the 86% of women who took at least one drug, the average number was nearly three drugs, including iron and

vitamins (range 1 to 15).[8] A 1986 study in the UK showed that about 35% of women took drugs (excluding iron and vitamin supplements and drugs used during labour) at least once during pregnancy, although only 6% took a drug during the first three months of pregnancy – the time at which the risk of a drug causing deformities in the fetus is at its greatest.[9] A 1985 survey in the USA showed that about 45% of pregnant women took at least one prescription drug during pregnancy and many more used drugs bought over the counter.[10] A 1987-8 study carried out in the Netherlands found that 86% of women took at least one drug (including iron and vitamins) during pregnancy. The average was just over four drugs.[11]

Many factors contribute to drug use in pregnancy. The "pill for every ill" mentality extends into pregnancy. Often, medicines are taken before the pregnancy has been confirmed. Some of this use is fostered by doctors and the pharmaceutical industry. For example, the number of prescriptions written in the USA in the late 1980s for the highly teratogenic drug, isotretinoin, bore little relation to the number of cases of cystic acne, its only indication. Instead the drug was being prescribed for acne vulgaris, the common, milder form of acne.[12]

Pregnancy itself has come to be seen more as a disease state than as a normal, healthy, condition. In such circumstances, medical intervention becomes virtually inevitable. This "medicalisation" of pregnancy means that women lose control of decisions affecting them. Often, they are not given information when they need it, and they can be misled into thinking that intervention in pregnancy is the normal way to cope with the problems that arise. Clinical pharmacologist Dr Joe Collier says that most pregnant women who go to hospital in the UK to have their babies are given some form of sedation the night before delivery. "Who are the drugs really for – the mother-to-be, her baby, or the medical staff who want a quiet night?"[13]

Health workers often lack the information they need to prescribe a rational course of treatment during pregnancy. The information provided by the drug industry is often unhelpful. For example, "in most countries where isotretinoin and etretinate are available, there are no formal programmes which systematically educate physicians and patients about the teratogenic hazards of these agents and, at the same time, attempt to assess the effectiveness of these interventions."[14] (See the box on isotretinoin on page 128.) More generally, companies include a standard protection line in drug information that simply states that "safety for use during pregnancy has not been established".[15]

Usually, a lack of reliable, objective information on drugs is the norm in developing countries. However, even in industrialised countries, contradictory information is given about drug use. For instance, in Italy in 1992, product information on tretinoin cream does not mention the risk of teratogenicity, whereas the *Physicians' Desk Reference* in the USA warns women to use the product in pregnancy only if absolutely necessary.[16]

Overall, too little is known about the effects of drugs taken in pregnancy. As the American

Table 7A-1
Australian Risk Classification System

Category	Description
A	Drugs which have been taken by a large number of pregnant women and women of childbearing age without an increase in the frequency of malformation or other direct or indirect harmful effects on the fetus having been observed.
B	Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. As experience of effects of drugs in this category in humans is limited, results of toxicological studies to date (including reproduction studies in animals) are indicated by allocation to one of three subgroups: B1 Studies in animals have not shown evidence of an increased occurrence of fetal damage. B2 Studies in animals are inadequate and may be lacking, but available data show no evidence of an increased occurrence of fetal damage. B3 Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.
C	Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.
D	Drugs which have caused an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.
X	Drugs that have such a high risk of causing permanent damage to the fetus that they should not be used in pregnancy or where there is a possibility of pregnancy.

Source: Australian Drug Evaluation Committee, *Medicines in Pregnancy*, Canberra, Australian Government Publishing Service, 1989, pp1-4

Medical Association (AMA) notes, "for many drugs, particularly new ones, little or no information is available on use during pregnancy."[17] (See the box below about efforts to develop an effective database on drugs used during pregnancy and childbirth.)

According to a UK consumer guide on medicines, "it is probably best to try and avoid taking any non-essential drugs in pregnancy or if you are trying to become pregnant.... We really know little more than that some drugs may produce abnormalities (teratogenesis) and that these are more likely when the drug is taken within the 12 weeks after conception."[18]

After birth, the newborn baby is less able than the adult to metabolise and excrete certain drugs and is hence more susceptible to their undesirable effects.[19] Some drugs can become concentrated in the mother's milk, such as iodine, which can then produce goitre in the baby; some tranquillisers such as diazepam can produce lethargy and weight loss in the baby and oral anticoagulants can produce bleeding. There are many other examples, and generally because there is "insufficient information available" on the effect of drugs in breast milk, "any drug should be taken with caution by breastfeeding mothers".[20]

A clear framework for deciding which drugs to prescribe or use during breastfeeding is difficult to develop. A starting point is to be certain that the drug is really needed by the mother. Other questions involve whether the drug would be absorbed by the baby if it is present in breast milk and, if so, whether it would harm the baby. The short answer is that any drug in the milk will be absorbed and, in therapeutic doses, would be likely to have a harmful effect. With most drugs, therapeutic dosage levels are unlikely to occur in breast milk.[21] However, a few drugs, such as iodides, may be concentrated in the milk, causing toxicity.[22] Table 7A-2 lists some drugs which have been identified as potentially hazardous while breastfeeding.

Conditions when drugs might be used

There are four main types of conditions arising during or around the time of pregnancy when drugs are often used. These are:

- infertility, when drugs may be used to stimulate ovulation;
- acute conditions that arise during pregnancy (pain and fever, infections, coughs and colds) or chronic conditions unrelated to pregnancy (asthma, epilepsy, diabetes);
- conditions commonly related to pregnancy (morning sickness, hypertension, anaemia); and
- complications of pregnancy and labour (threatened miscarriage, premature labour, toxaemia, pain in childbirth).

Table 7A-2
Drugs to avoid or use with caution* during breastfeeding

Avoid	amantadine, anticancer drugs, bromocriptine, chloramphenicol, ergot alkaloids, clemastine, gold salts, iodine, lithium, phenindione, thiouracil
Caution	alcohol, aminophylline, amiodarone, aminoglycoside, antibiotics, anthraquinones, aspirin, atropine, barbiturates, benzodiazepines, beta-blockers, calciferol, carbimazole, chlorpromazine, cimetidine, clindamycin, corticosteroids, diuretics, indomethacin, isoniazid, laxatives, meprobamate, methyldopa, metronidazole, nalidixic acid, nitrofurantoin, opioid analgesics, oral contraceptives, penicillins, phenobarbitone, phenylbutazone, reserpine, sex hormones, sulphonamides.

* **Note:** Using a drug with caution means to avoid use if possible. If the drug is needed, seek additional information on how to minimise risks. Some drugs should only be used at low doses or on a short-term basis. For many drugs, insufficient evidence is available to establish safety. Drugs not listed in this box are not necessarily safe; obtain more information before prescribing or taking any drug during breastfeeding.

Sources: Lewis, P.J., and Hurden, E.L., "Breast feeding and drug treatment", in: Hawkins, D.F. (ed.), *Drugs and Pregnancy*. London, Churchill Livingstone, (2nd edn) 1987, p318; Laurence, D.R. and Bennett, P.N., *Clinical Pharmacology*. Edinburgh, Churchill Livingstone, (6th edn), 1987, pp131-2

A database on beneficial drugs

Randomised clinical trials (RCTs) that compare a drug to an inactive treatment, or to a treatment whose effectiveness is known, are the best source of information for making rational decisions about therapy. Such trials can show whether a drug is beneficial, which people benefit, and by how much. It is, however, time consuming and difficult to find the reports of all the relevant RCTs that have been performed and to review them systematically and reliably. The field of pregnancy and childbirth is the first for which a database of regularly updated systematic reviews exists – the Cochrane Collaboration Pregnancy and Childbirth Database.[1] It contains nearly 600 detailed reviews on topics such as: drug treatment of hypertension in pregnancy; routine iron supplementation in pregnancy; periconceptional folate in high-risk mothers; antibiotics for asymptomatic bacteriuria; and brief corticosteroid therapy before pre-term delivery (to reduce the risk of respiratory distress syndrome in the baby). The database is expected to be of great value to pregnant women considering treatment options, as well as to doctors and midwives. It is worth emphasising, however, that the adverse effects of treatments often cannot be reliably identified or predicted in RCTs.

Note: A paperback guide based on the database was published in 1990: Enkin, M., Keirse, M. and Chalmers, I., *A Guide to Effective Care in Pregnancy and Childbirth*, Oxford, Oxford University Press, 1990. The database itself is produced twice a year on computer disks. [See the section on *Useful Addresses* for ordering information.]

Isotretinoin: warning about risk

Less than a year after the introduction of isotretinoin* in 1982 in the USA, the manufacturer, Hoffman-La Roche, had reported seven spontaneous abortions and five birth defects associated with use of the drug during pregnancy.[1] By 1991, 91 serious cases of birth defects had been reported in the USA.[2] Because of the general under-reporting of adverse effects, some estimates suggest that a more realistic number is nearer 240.[3]

During 1983, both Roche and the US FDA began to take steps to alert physicians to the dangers, including sending letters, updating information brochures, and issuing warnings in the FDA's bulletin. However in 1988, public concern about the drug and about continuing cases of it being used by pregnant women led to public hearings and the introduction of an even stronger programme of education about the drug's use. The programme includes an elaborate consent form, detailed explanation to the patient about the hazards of pregnancy, a pregnancy test, confirmation that the woman can and will take necessary contraceptive measures, and careful selection of patients who meet the treatment criteria: only those with severe, disfiguring cystic acne that is not responsive to other therapies. Before the introduction of the programme, other non-labelled indications for isotretinoin were "widely accepted" by physicians.[4] One estimate placed the magnitude of overuse of the drug at some 15 to 20 times greater than the number of women with severe recalcitrant cystic acne.[5] When the drug was first introduced, there was no demand that a pregnancy test be performed, and the drug was heavily promoted to doctors, "minimizing the importance of the risks".[6]

Since the programme was introduced, there have been two further modifications to strengthen the warnings in 1990 and 1991 and a survey of use of the drug in women has been carried out, under contract from Roche. Although it found that virtually all women enrolled in the educational programme were aware of the dangers of using the drug during pregnancy, 37% of women did not have a pregnancy test before starting on the drug. There was also evidence of "a large amount of reckless and dangerous prescribing" with nearly one-third of the women of child-bearing age surveyed showing no sign of acne cysts. These findings led the Public Citizen Health Research Group to repeat its call for the drug to be restricted to specifically registered doctors.[3] In the UK, the drug is available only through hospital pharmacies for use in hospitals and hospital clinics and should be given by or under the supervision of a dermatologist.[7]

***Note:** Isotretinoin is marketed by Roche as Accutane in the USA, and as Roaccutane in the UK and many other countries.

Sources:

1. Mitchell, A.A., "Oral retinoids: What should the prescriber know about their teratogenic hazards among women of child-bearing potential?", *Drug Safety*, Vol 7, No 2, 1992, pp79-85
2. Anon., "FDA cm'ttee on Accutane labelling", *Scrip*, No 1623, 7 Jun 1991, p26
3. Anon., "Roche elaborates on US Accutane warnings", *Scrip*, No 1537, 3 Aug 1990, p27
4. Stern, R.S., "When a uniquely effective drug is teratogenic: the case of isotretinoin", *New England Journal of Medicine*, Vol 320, No 15, 13 Apr 1989, pp1007-9
5. Faich, G. and Rosa, F., "When a uniquely effective drug is teratogenic: the case of isotretinoin" (letter), *New England Journal of Medicine*, Vol 321, No 11, 14 Sep 1989, pp756-7
6. Anon., "Acne, Accutane, abortions and life-threatening birth defects", *Health Letter*, 12 May 1988
7. BMA and the Royal Pharmaceutical Society of Great Britain, *British National Formulary*, London, BMA and The Pharmaceutical Press, No 23, Mar 1992, p405

Serono advertises two drugs to "respond to the challenge of infertility" without mentioning specific indications; QIMP, Pakistan, Sept 1988-Feb 1989.

Drugs for infertility

Drugs are only useful in the treatment of female infertility when the cause is some form of hormone deficiency that prevents ovulation. This accounts for a minority of cases of infertility. WHO points out that one-third of all infertility among couples occurs because of an abnormality in the male partner. In women, the commonest cause of infertility is damage to the Fallopian tubes as a result of infection.[23] In developing countries, between 50 and 80% of infertility in women is attributable to reproductive tract infections.[24] Even where drugs to induce ovulation are indicated, pregnancy is likely to occur in only approximately 30% of cases.[25] If pregnancy is successful, multiple births are more likely.[26]

The main drugs used are clomiphene citrate, follicle stimulating hormone (FSH), human menopausal gonadotrophin (HMG), and human chorionic gonadotrophin (HCG), sometimes in combination. As with all drugs taken around the time of conception, there is a theoretical possibility of causing damage to the fetus.[27] The effects of clomiphene on early gestation, however, "are not understood" and pregnancy should be ruled out before it is administered.[28] Particular concern has been raised because of the structural similarities between clomiphene and diethylstilbestrol (DES). Some experimental studies have shown that high doses of clomiphene can cause changes to fetal vaginal tissues similar to those that occur with DES. Clomiphene could have a teratogenic effect if taken just before conception because metabolites of the drug may still be present during early pregnancy.[29] There is also some evidence of abnormalities among children born to women who inadvertently took clomiphene during the first six weeks after conception.[30] The risk of ovarian cancer among women taking clomiphene or gonadotrophins is another cause for concern (see box above).

Fertility drugs and ovarian cancer: a cause for concern?

In April 1993, *The Lancet* published a report on a possible relationship between the use of fertility drugs and the development of ovarian cancer. Dutch researchers reported that 12 out of 5250 women who were treated for infertility with clomiphene citrate and/or gonadotrophins developed granulosa-cell tumours, a form of ovarian cancer. The age of the women varied from 25 to 38. Half the women sought fertility treatment because they developed amenorrhoea following the use of oral contraceptives.

Although the authors stated that they could not "prove the existence of a causal relationship" because the number of women studied was small for such a rare form of cancer, they pointed out that this was a much higher rate of ovarian cancer than would be expected in this age group. They urged caution in prescribing ovarian stimulants.

The Dutch Society for Obstetrics and Gynaecology appears to have come to different conclusions. Dr H. Evers, a gynaecology professor, acted as the Society's spokesperson after the report was released. He commented in a local newspaper that "there is no reason for concern". He said that "tens of millions of women all over the world have been treated with these hormones. I find it a comforting thought that nobody ever noticed the development of this type of cancer in such a large group... these researchers apparently found a few patients with granulosa cell tumours. They continued to look and out of a group of 5250 they picked these 12. Gynaecologists who possibly treated thousands of women with hormones and who did not find granulosa-cell tumour were left out of this study. No, there is no reason for concern."

Sources:
Willemsen, W., Kruitwagen, R., Bastiaans, B., Hanselaar, T., and Rolland, R., "Ovarian stimulation and granulosa cell tumour", *Lancet*, Vol 341, 17 April 1993, pp986-8
Kaashoek, P., "Mogelijk eierstokkanker door vruchtbaarheidsmedicijn", *Eindhovens Dagblad*, 1 May 1993

Drugs for acute or chronic conditions

If possible, it is best to avoid drug use for acute or chronic conditions during pregnancy. Where it is not possible, the choice should be those drugs that have been in use for the longest time with no evidence of harmful effects.

Analgesics, non-steroidal inflammatory drugs (NSAIDs), antibiotics, cough and cold remedies, and a variety of psychotropic drugs are among the products often prescribed or used for acute conditions during pregnancy. NSAIDs, antimicrobials, and some psychotropic drugs might also be prescribed for chronic conditions, along with products such as corticosteroids and other anti-asthmatics, insulin and hypoglycaemics, and anticonvulsants.

Analgesics

Analgesics, if needed, should be taken at as low a dose and for as short a time as possible. Simple pain killers are preferred. Paracetamol is the drug of choice if a pain killer is needed during pregnancy.[31]

Estimates for the use of aspirin in pregnancy in the USA range from 10 to 45% of women, with most use occurring in the first trimester of pregnancy.[32] Although animal studies have shown that salicylates (aspirin-like drugs) can cause birth defects, there is no conclusive evidence that they cause malformations in humans. However, if taken late in pregnancy, aspirin can inhibit uterine contraction, lead to complications during delivery, and can cause neonatal and maternal bleeding.[33] It is generally recommended that aspirin should be avoided completely in pregnancy.[34]

However, recent investigations suggest that there may be a therapeutic role for low-dose aspirin among a *limited* number of women at risk from pregnancy-induced hypertension or poor fetal growth.[35] Nonetheless, even after these findings, the US Food and Drug Administration (FDA) ruled that labels of over-the-counter products containing aspirin should warn women not to use aspirin during the last three months of pregnancy unless told to do so by a doctor.[36] As one of the studies points out, even though there may be some justification for a restrained use of aspirin, "massive use of aspirin by millions of pregnant women yearly cannot be recommended".[37]

Migraine medications such as ergotamine are contraindicated in pregnancy.[38] Narcotic analgesics may depress the brain and respiration of the baby, particularly when given to relieve the pain of childbirth.[39]

Like aspirin, NSAIDs can inhibit uterine contractions and lead to difficult labour. Drugs such as indomethacin, ibuprofen and naproxen should be avoided at least in the last three months of pregnancy.[40]

Table 7A-3
Safety of antibiotics during pregnancy

While all drugs, including antibiotics, should be avoided if possible during pregnancy, the treatment of infections may be necessary for the health of either the mother, the baby or both. In such cases, the following guideline indicates which antibiotics are considered to be least harmful.

Antibiotic	Trimester in which antibiotic is considered safe	Comments
Aminoglycosides	Third	risk of damage to hearing increases in second trimester; gentamicin is considered safest
Cephalosporins	All	avoid cefamandole, moxalactam, cefotetan and cefoperazone
Chloramphenicol	First and second	can cause "grey baby" syndrome
Erythromycin	All	avoid erythromycin estolate which may cause maternal hepatitis
Isoniazid	None	considered the safest of all anti-tuberculosis drugs, but prophylaxis should be postponed until after delivery, due to risk of hepatitis; animal studies have shown the drug to be embryocidal
Penicillins	All	studies of combination forms with clavulanic acid have not demonstrated toxic effects
Quinolones	None	diseases of the joints have been noted when used in immature animals; nalidixic acid has been used safely in second and third trimesters but should be discontinued at labour
Sulphonamides	Second	possible antifolate effects in first trimester; risk of brain damage caused by bile pigment (bilirubin) in third trimester
Tetracyclines	None	maternal risk of liver, pancreas or kidney diseases; fetal risk of teeth discoloration, abnormal development of bone tissues, retarded bone growth
Trimethoprim	First and third	folate antagonism

Source: adapted from Lynch, C.M., Sinnott IV, J.T., et al, "Use of Antibiotics During Pregnancy", *American Family Physician*, Vol 43, No 4, Apr 1991, p1367

There is, however, some indication that indomethacin may be useful in the treatment of premature labour, provided that the fetus is carefully monitored.[41] (See the box on page 134 about ritodrine – another drug used for treating premature labour.)

Antibiotics

A range of epidemiological studies carried out over the past 30 years show that an antibiotic is taken by anywhere from one out of every six to one out of every two pregnant women.[42] Most of those studies have looked at drug use in industrialised countries. However, the dangers of poverty-related infection and the generally excessive misuse of antibiotics in developing countries only serve to highlight the need for a critical look at the consumption of antibiotics during pregnancy.

Well-known antibiotics which have been used for years are usually effective and more recent drugs can be reserved for infections that do not respond. "There is little indication to use the latest trivial molecular modification whose side effects in pregnancy are ill-documented."[43] The penicillins and cephalosporins are considered the antibiotics of choice for most infections in pregnancy. Table 7A-3 highlights the evidence on safety of antibiotics in pregnancy.

Metronidazole is not recommended in early pregnancy, as animal studies demonstrated a possible risk of cancer;[44] however, the animal research is controversial, and it is generally thought to be safe for use in the last six months of pregnancy.[45]

Isoniazid is considered to be the safest antituberculosis drug for use during pregnancy, but prophylactic use should be avoided. Rifampicin should be avoided during the first three months.[46]

Antimalarial drugs such as pyrimethamine with either dapsone or sulfadoxine are no longer recommended for use. Primaquine should be avoided during pregnancy.[47] High doses of quinine can cause fatal congenital malformations. Chloroquine is the drug of choice for treatment or prevention of malaria in pregnancy, but has been associated with rare cases of damage to the eyes.[48] There is also the problem of increasing resistance to these standard therapies for malaria. Mefloquine has shown some promise in treating primaquine or chloroquine resistant malaria and may also be acceptable in pregnancy, but it has not yet been studied sufficiently to be certain about its effect during pregnancy.[49] It should probably not be used during the first three months.[50]

Cough and cold remedies

As a large proportion of cough and cold remedies contain ineffective ingredients, some of which are potentially harmful, their use should be avoided generally, but especially so during pregnancy. Some proprietary cough medicines obtainable without prescription contain iodine. The use of iodine (or an iodide) and medicines containing iodine is contraindicated in pregnancy.[51] In Brazil in 1988, 50 out of 315 (16%) cough and cold preparations contained an iodide.[52] In Africa and the Caribbean during 1991, Wallace was marketing Bepro cough syrup that contained calcium iodide. The product listing in prescribing guides gave no warning about avoiding use in pregnancy.[53]

Psychotropics

Anxiety, insomnia and depression may occur during pregnancy. However, use of drugs to control these symptoms should be avoided if possible. "Other forms of treatment are important and include support from staff or self-help groups, psychological treatments such as relaxation exercises or cognitive therapy, and mobilisation of community resources."[54]

Very little is known about the effects of psychotropic drugs in pregnancy. While no definite evidence exists to link the use of barbiturates or benzodiazepines to birth defects, "there are few valid indications for using these drugs in early pregnancy and it is possible that their use may be associated with a small increased risk of malformation".[55] Diazepam use, for example, has been linked to an increased risk of cleft lip and palate in some studies.[56] Similar reports of malformations have been associated with the use of barbiturates, chlordiazepoxide and meprobamate.[57]

In later pregnancy, when brain cells are developing, psychotropic drugs can affect neurotransmitters and may produce subtle changes which result in functional disturbance and behavioural difficulties in later life.[58]

Long-term exposure to diazepam or any of the benzodiazepines can also cause withdrawal symptoms. Sedation and poor feeding in the newborn can follow use of diazepam before delivery. According to the AMA, "withdrawal symptoms and signs can be expected in infants born to mothers who are physically dependent on benzodiazepines during the last trimester".[59]

As one textbook on the use of drugs in pregnancy points out:

> "No sedative is entirely free of effects on the newborn and it would seem prudent to avoid repeated doses of any of this group of drugs in late pregnancy unless good indications exist."[60]

Drugs for chronic conditions

Some drugs are given as therapy for continuing conditions. Corticosteroids are often used in pregnancy for asthma patients. Although animal studies demonstrate a teratogenic effect, human experience suggests that the risk is small and may be dose related. Where possible, corticosteroids should be

avoided in early pregnancy and the lowest possible doses used at other times.[61] Drugs used to treat respiratory conditions should also be used with caution. Sympathomimetics (such as noradrenaline, aminophylline) may harm the fetus, and beta adrenoceptor stimulants (like salbutamol) should be avoided late in pregnancy. However, generally, in normal doses none of the usual anti-asthma drugs harm either the mother or fetus.[62]

In epilepsy, anticonvulsants (carbamazepine, phenytoin, primidone or valproic acid) are usually needed, although all these drugs are possible teratogens. Valproic acid, in particular, has been linked to an increased risk of spina bifida.[63] In general, where anticonvulsant therapy is essential, a single drug rather than a combination of drugs should be used to minimise risk.[64] According to *The Lancet*, epileptic seizures pose a greater overall risk to mother and baby than do anti-epileptic drugs used properly.[65]

Although there is no convincing evidence that oral hypoglycaemic agents will damage the fetus, these drugs may cause hypoglycaemia in the newborn. In the USA, oral hypoglycaemic agents are contraindicated during pregnancy.[66] Pregnant diabetic women not controlled by diet alone should be treated with insulin.

All antithyroid drugs can produce goitre in a small number of infants, so caution and careful monitoring of newborns is recommended.[67]

Pregnancy-related conditions

Some drugs are given in pregnancy for relatively transient problems. Drug treatment is rarely if ever needed for those conditions commonly related to pregnancy. Health workers and pregnant women need information about non-drug solutions instead of drugs.

Common complaints such as heartburn, indigestion and constipation are best treated simply. Diet changes, fresh air or sleep are the safest remedies.[68] Changes in dietary habits or simple antacid preparations are recommended for stomach problems, while fluid or roughage is best for constipation. Preparations which stimulate bowel activity may also stimulate uterine contraction and are contraindicated in pregnancy.[69]

Morning sickness occurs in about 50% of pregnancies during the first three months – a time that coincides with the maximum risk for teratogenic effects.[70] Antihistamines are frequently prescribed or recommended, even though there have been some concerns expressed about teratogenic risk.[71] However, according to the *British National Formulary*, "nausea in the first trimester of pregnancy does *not* require drug therapy".[72]

Circulatory and renal changes during pregnancy can often create hypertension. However, drug treatment is not necessarily the best way to deal with pregnancy-induced hypertension. Bed rest and dietary measures are often sufficient. Underlying or "essential" hypertension that was present before pregnancy has been treated with a wide variety of drugs: sedatives, hypotensives, diuretics, heparin or anticonvulsants. The preferred drug has usually been methyldopa.[73] Women who are already suffering from hypertension and are using an ACE-inhibitor when they become pregnant should be switched to a different antihypertensive because of reports of fetal death when ACE-inhibitors are used in later pregnancy.[74]

Iron and vitamin supplements

Vitamins and minerals, particularly iron, are regularly prescribed or taken during pregnancy. Often they are taken in the belief that because they are "natural" substances, they are harmless. However, that is not the case. For example, vitamin A and its analogues have long been known to be teratogenic in animals.[75] An overdose of iron can be "extremely dangerous" and can lead to dangerously lowered blood pressure, and congestive heart failure.[76] A leading guide to women's health makes the point that "taking large doses of vitamins is not wise in pregnancy. Vitamins are active chemical agents and should only be taken to make up a definite deficiency."[77] There is no evidence to suggest that the routine administration of vitamins to generally healthy pregnant women offers any advantage whatsoever.[78] As the AMA points out:

> "The routine prescription of multivitamin and mineral supplements for pregnant and lactating women is common but generally unnecessary. A well balanced diet designed to meet the needs of pregnant and lactating women minimises the need for supplementation."[79]

One controversial subject is the question of the "need" for iron supplementation in pregnant women. Most pregnant women have lower iron levels in the blood, so it has been assumed that supplementation is necessary. However, the reduction in iron levels is a natural process in pregnancy because the mother's blood volume is increased in order to supply the growing baby. The human body also has large reserves of iron in the liver and bone marrow and during pregnancy these stores are drawn upon.

There is no evidence that prophylactic treatment with iron in pregnancy has any significant effect on the health of either mother or child. In fact, iron supplements may do more damage than good. Iron preparations often cause gastrointestinal disturbances. They are reported to be the commonest causes of vomiting in pregnancy. They can also cause either constipation or diarrhoea which frequently lead women to stop taking them. Prophylactic oral iron is unnecessary for the majority of healthy pregnant women in an industrialised country. The daily

dietary intake of iron is usually sufficient to maintain sufficient iron stores in all but a tiny percentage – perhaps as low as 2% – of women in most industrialised countries. It is only women who are already anaemic or have depleted iron stores at the start of pregnancy – perhaps due to chronic nutritional deficiency, heavy menstrual blood loss, or repeated pregnancies – who need routine iron supplements.[80]

However, the situation differs in developing countries. The World Health Organization (WHO) estimates that more than 700 million people suffer from iron-deficiency anaemia worldwide. It suggests that all pregnant women in developing countries should receive iron supplements during the last four to five months of pregnancy.[81] Iron supplementation, however, is a curative approach. Efforts to improve general nutrition and ensure that people have access to an affordable supply of food which meets all their nutritional needs are more important.[82]

Folate (folic acid) deficiency – the second most important cause of anaemia during pregnancy after iron deficiency – is frequent in developing countries. Research shows that folate supplementation is effective in improving pregnancy outcomes in developing countries or in populations whose socio-economic status is low.[83] Folic acid supplementation may benefit both mother and baby. A deficiency of folic acid can lead to a severe form of anaemia (megaloblastic anaemia) in women and can cause congenital abnormalities in the fetus such as spina bifida and other failures of the neural tube – the tissue structure from which the brain and spinal cord develop – to close properly. Identifying women at risk and ensuring they begin folic acid supplementation before pregnancy has successfully reduced the incidence of neural tube defects.[84] This is now recommended practice in the USA and the UK. In both countries, it is also recommended that *all* women receive a small amount (0.4mg) of folic acid supplement daily before and during the first 12 weeks of pregnancy.[85]

Although there may be cases where both iron and folic acid are required, there is little justification for using combination preparations, and certainly no justification for iron together with multivitamins. Goodman and Gilman's textbook on pharmacology points out that

> "it is particularly undesirable to use [iron] preparations that contain other compounds with therapeutic actions of their own, such as vitamin B12, folate, or cobalt, since the patient's response to the combination cannot be easily interpreted. Despite the straightforward nature of therapy with iron, it is discouraging to see the frequency with which expensive preparations with worthless additives are prescribed."[86]

Prescribing in pregnancy

The editor of one leading book on drug use in pregnancy, Dr D.F. Hawkins, a consultant obstetrician, gynaecologist, and pharmacologist suggests four basic rules for prescribers.

1. Review all patients with medical disorders before they conceive, regarding every woman of reproductive age as a potential antenatal patient, and encouraging them to attend for counselling before planning a pregnancy.
2. Question the real need for any drug in pregnancy, giving due consideration to alternative methods of treatment.
3. Review all drug regimens in pregnancy to see how careful therapeutics and good control can minimise risks.
4. Use medicines that have been widely employed in pregnancy for years in preference to the latest drugs.

Source: Hawkins, D.F. (ed.), *Drugs and Pregnancy*, London, Churchill Livingstone, (2nd edn) 1987

Complications in pregnancy or labour

For pregnancy complications, only drugs with proven efficacy in improving survival rates and/or the health of the baby or mother should be used. During labour and delivery, the routine use of drugs should be discouraged and interventions that increase the need for drugs to reduce pain should be avoided unless there is proof of effectiveness in improving survival rates and health.

Diethylstilboestrol (DES), a synthetic oestrogen, was first used to prevent miscarriage but was found to be ineffective and unsafe. However, DES became widely used with tragic results. Daughters of women who used DES during pregnancy may develop a rare form of vaginal and cervical cancer at a young age. This occurs in between one in 1000 to one in 10,000 women exposed prenatally. DES has also caused malformations of the reproductive organs in women and, to a lesser extent, in men exposed before birth. Experts now agree that there is no indication for the use of DES or any oestrogen in pregnancy.[87] Oestrogens can cause masculinisation of the female fetus if given over a long period during pregnancy and, rarely, feminisation of the male fetus.

Even Sir Charles Dodds, the inventor of DES, was cautious about the use of hormones in women because their reproductive cycle was "far too delicate a mechanism to bombard with exotic, powerful, foreign chemicals".[88]

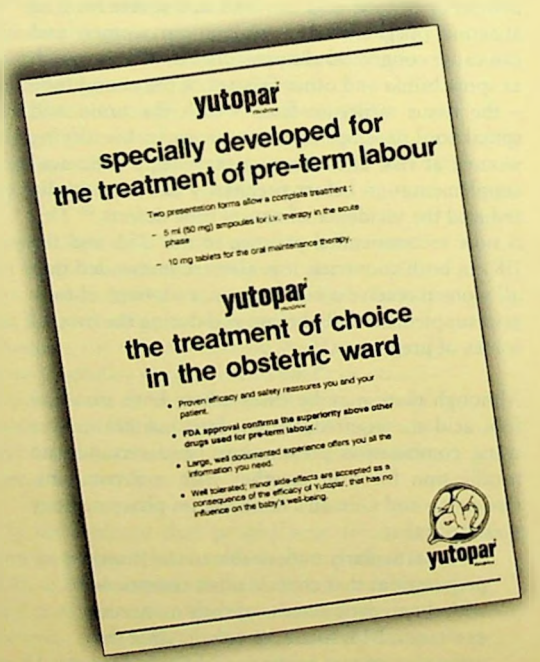
Ritodrine: a risk to mothers?

In July 1992, a 20-year-old pregnant woman, Deborah Coram, died when a drug used to inhibit premature labour, ritodrine (Yutopar), was incorrectly mixed by hospital staff in Chatham, UK. The cause of death was attributed to a chest infection that result from the side effects of the drug. The drug was mixed in a saline solution rather than the dextrose solution recommended by the manufacturer. None of the doctors questioned at a coroner's inquest knew of the drug's adverse effects if it was wrongly mixed. This is not surprising, as neither the *Data Sheet Compendium* nor the *British National Formulary* provide a warning against the use of a saline mix. The *Data Sheet Compendium* does indeed recommend a dextrose solution, but the manufacturer, Duphar, has now issued new guidelines banning the use of saline solutions with the drug.[1]

The US FDA's fertility and maternal health drugs advisory committee reviewed ritodrine in October 1992. It concluded that the injectable form *is* effective in improving the course of preterm labour, but that oral ritodrine "is not effective in maintaining remission of preterm labour at the current recommended doses" and "does not have a place in obstetric medicine at its current dosage levels".[2] This is expected to have considerable impact on the billion dollar market for the drug in the USA, where an estimated 100,000 women a year use ritodrine.[3]

A paper published in July 1992 in the *New England Journal of Medicine* reported on a double-blind trial of ritodrine in Canada which found that ritodrine had "no beneficial effect on fetal or neonatal mortality, or on the incidence of pre-term delivery". An editorial in the same issue of the Journal drew attention to the 95 reports of fluid in the lungs (pulmonary oedema) in the USA since ritodrine's approval in 1980, and the association of the drug with unusual heart rhythms. At least 14 maternal deaths have been recorded. Because of these "substantial maternal risks" and the "vanishingly small neonatal benefits", the editorial called for a reappraisal of ritodrine.[4]

Ritodrine (Yutopar), advertised in Pakistan in 1988 as having "proven efficacy and safety", with "minor side-effects"



Sources:
1. Anon., "Drug mixing error is blamed for pregnant woman's death", *Guardian*, 22 Dec 1992, p3 (See also: ABPI, *ABPI Data Sheet Compendium 1988-89*, London, Datapharm Publications, 1988, pp449-50; BMA and the Royal Pharmaceutical Society of Great Britain, *British National Formulary*, London, BMA and The Pharmaceutical Press, No 23, Mar 1992; pp279 and 520)
2. Anon., "FDA committee reviews Astra's ritodrine", *Scrip*, No 1769, 10 Nov 1992, p27
3. Anon., "Labour drug ritodrine proves ineffective", *New Straits Times* (Malaysia), 4 Aug 1992, p31 (based on a *New York Times* report)
4. Anon., "Ritodrine's risk/benefit in preterm labour questioned", *Scrip*, No 1744, 14 Aug 1992, p20

The tragedy with DES is "an example of what has happened and can happen unless we are vigilant".[89] It also highlights the difficulty in assessing the adverse effects of drug use during pregnancy. Babies exposed to DES were fine and healthy at birth. The effects only became evident after puberty. The initial invisibility of these effects reinforces the need to avoid the unnecessary use of drugs in pregnancy.

[See the section on *DES* for further information.]

Progestogens – such as ethisterone, norethisterone, and methyltestosterone – may cause congenital defects and have virilising effects if taken in early pregnancy. These drugs have been used to treat threatened or habitual abortion, but their efficacy is doubtful, and such use is not recommended.[90]

Oestrogens and progestogens, when used in low doses, as in the contraceptive pill, have been associated with fetal damage. The VACTERL (vertebral, anal, cardiac, tracheal, oesophageal, renal and limb malformations) syndrome of defects has been reported due to exposure to sex steroids during pregnancy. However, it is thought that the risk is small.[91]

One danger of any hormone treatment is that it can actually mask the onset of pregnancy, so that the woman is inadvertently put at extra risk by continuing the treatment. Unfortunately, many high-dose oestrogen-progestogen (EP) drugs are still sold in developing countries without sufficient warning of their dangers. Too often, these products are misused in attempts to provoke an abortion. This is particularly a problem where safe, low-cost legal abortion is not available. While regulatory and educational efforts are necessary to control availability and misuse of ineffective abortifacients, removing the demand by ensuring access to legal abortions is more likely to have the greatest effect.

[See the section on *EP Drugs* for further information.]

Avoiding unnecessary drug use

Overall, caution with drugs during pregnancy must be stressed. According to the *British National Formulary*:

> "No drug is safe beyond all doubt in early pregnancy.... Drugs should be prescribed in pregnancy only if the expected benefit to the mother is thought to be greater than the risk to the fetus, and all drugs should be avoided if possible during the first trimester."[92]

Unfortunately drug consumption in pregnancy is often needlessly and alarmingly high, exposing the fetus to risks of malformations or developmental problems.

Recommendations for action

1. Health authorities should develop information for women on drugs in common use during pregnancy, and on non-drug solutions for common health problems experienced during pregnancy.

2. Similar information should be prepared for prescribers and dispensers of drugs, along with notices to be prominently displayed to remind about the need for caution in pregnancy.

3. There should be international implementation of uniform categories for labelling drugs that clearly identify relative risks in pregnancy.

4. A clear, understandable and universally recognised graphic symbol illustrating that the product should not be used in pregnancy should be developed and placed on *all* prescription and over-the-counter drugs whose safety in pregnancy has not been verified.

References:

1. Anon., "Acne, Accutane, abortions and life-threatening birth defects", *Health Letter*, 12 May 1988
2. Lynch, C.M., Sinnott, J.V., et al, "Use of antibiotics during pregnancy", *American Family Physician*, Vol 43, No 4, Apr 1991, pp1365-8
3. Niebyl, J.R., "Drugs and related areas in pregnancy", *Zent.bl. Gynakol.*, Vol 113, 1991, pp375-88
4. Laurence, D.R. and Bennett, P.N., *Clinical Pharmacology*, London, Churchill Livingstone, (6th edn), 1987, p85
5. AMA, *Drug Evaluations*, Philadelphia, W.B. Saunders Co., (6th edn) 1986, pp41-50
6. Martínez-Frías, M.L. and Salvador, J., "Megadose vitamin A and teratogenicity", *Lancet*, No 8579, 30 Jan 1988, p236
7. Gilman, A.G., Rall, T.W., Nies, A.S., and Taylor, P., *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, New York, Pergamon Press, (8th edn) 1990, p13
8. Collaborative Group on Drug Use in Pregnancy, "Medication during pregnancy: an intercontinental cooperative study", *International Journal of Gynecology and Obstetrics*, Vol 39, 1992, pp185-96
9. Rubin, P.C. (ed.), *Prescribing in Pregnancy*, London, British Medical Journal, 1987, p1
10. Whittle, M.J. and Hanretty, K.P., "Identifying abnormalities", in: Rubin, op cit, pp8-18
11. de Jong-van den Berg, L.T.W., van den Berg, P.B., et al, "Investigating drug use in pregnancy: methodological problems and perspectives", *Pharmaceutisch Weekblad Scientific Edition*, Vol 13, No 1, 1991, pp32-8
12. Fugh-Berman, A., "On the FDA's recommendations for the use of isotretinoin", *The Drug Monitor* (Philippines), Vol V, No 10, Oct 1990, pp127-8
13. Collier, J., *The Health Conspiracy*, London, Century Hutchinson, 1989, p15
14. Mitchell, A.A., "Oral retinoids: what should the prescriber know about their teratogenic hazards among women of child-bearing potential?", *Drug Safety*, Vol 7, No 2, 1992, pp79-85
15. Ledward, R.S., "Antimicrobial drugs in pregnancy", in: Hawkins, D.F. (ed.), *Drugs and Pregnancy*, London, Churchill Livingstone, (2nd edn) 1987, pp148-65
16. Camera, G. and Pregliasco, P., "Ear malformation in baby born to mother using tretinoin cream", *Lancet*, Vol 339, 14 Mar 1992, p687
17. AMA, op cit, p42
18. Parish, P., *Medicines: a guide for everybody*, London, Penguin (6th edn, revised), 1989, pp33-4
19. Henry, J. (ed.), *The British Medical Association Guide to Medicines & Drugs*, London, Dorling Kindersley, (2nd edn) 1991, p20
20. Parish, op cit, p34
21. Lewis, P.J. and Hurden, E.L., "Breast feeding and drug treatment", in: Hawkins, D.F. (ed.), *Drugs and Pregnancy*, London, Churchill Livingstone, (2nd edn) 1987, pp304-32
22. BMA and the Royal Pharmaceutical Society of Great Britain, *British National Formulary*, BMA and the Pharmaceutical Press, No 23, Mar 1992, pp517-21
23. Khanna, J., van Look, P.F.A., and Griffin, P.D. (eds), *Reproductive Health: a Key to a Brighter Future*, Geneva, WHO, 1992, p104
24. Jacobson, J.L., "Improving women's reproductive health", chapter 6 in: Brown, L.R., Brough, H., et al, *State of The World 1992*, London, Earthscan, 1992, pp83-99
25. Adashi, E.Y., Rock J.A., Sapp, K.C. et al, "Gestational outcome of clomiphene-related conceptions", *Fertility and Sterility* Vol 31, 1979, pp620-626, cited in: Jong-v.d. Berg, L.T.W., Comel, M.C., van den Berg, P.B., et al "Ovulation-inducing drugs: a drug utilization and risk study in the Dutch population." *International Journal of Risk and Safety in Medicine*, Vol 3, 1992, p107
26. Henry, J. (ed.), *The British Medical Association Guide to Medicines & Drugs*, London, Dorling Kindersley, (2nd edn) 1991, p160
27. Phillips, et al, op cit, p429
28. Gilman, A.G., Rall, T.W., Nies, A.S., and Taylor, P., op cit, p1397
29. Jong-v.d. Berg et al, 1992, op cit, p100
30. Rowland, RI, *Living Laboratories: Women and reproductive technology*, London, Lime Tree/Octopus, 1992, pp50-1.
31. Howden, C.W., "Treatment of common minor ailments" in: Rubin, op cit, pp19-25
32. Werler, M.M., Mitchell, A.A. and Shapiro, S., "The relation of aspirin use during the first trimester of pregnancy to congenital cardiac defects", *New England Journal of Medicine*, Vol 321, No 24, 14 Dec 1989, pp1639-42
33. Australian Drug Evaluation Committee, *Medicines in Pregnancy*, Canberra, Australian Government Publishing Service, 1989, p6
34. Howden, op cit, pp19-25
35. See for example: Elder, M.G., de Swiet, M., et al, "Low-dose aspirin in pregnancy", *Lancet*, No 8582, 20 Feb 1988, p410; Schiff, E., Peleg, E., et al, "The use of aspirin to prevent pregnancy-induced hypertension and lower the ratio of thromboxane A2 to Prostacyclin in relatively high-risk pregnancies", *New England Journal of Medicine*, Vol 321, No 6, 10 Aug 1989, pp351-6; Cunningham, F.G. and Gant, N.F., "Prevention of preeclampsia – a reality?", *New England Journal of Medicine*, Vol 321, No 9, 31 Aug 1989, pp606-7; Werler, et al, op cit, pp1639-42; Uzan, S., Beaufils, M., et al, "Prevention of fetal growth retardation with low-dose aspirin: findings of the EPREDA trial", *Lancet*, Vol 337, 15 Jun 1991, pp1427-31; Anon., "Aspirin beneficial in pregnancy", *Scrip*, No 1637, 26 Jul 1991, p27
36. Anon., "US FDA tightens aspirin warning", *Scrip*, No 1530, 11 July 1990, p22
37. Uzan, et al, op cit, pp1427-31
38. BMA and the Royal Pharmaceutical Society of Great Britain, op cit, p176
39. Hawkins, op cit, p79
40. Anon., "Drug use in pregnancy", *The Prescriber*, No 1, Jan 1992, p7
41. Moise, K.J., Huhta, J.C., et al, "Indomethacin in the treatment of premature labor", *New England Journal of Medicine*, Vol 319, No 6, 11 Aug 1988, pp327-31
42. Lewis, J.H., "Drug hepatotoxicity in pregnancy", *European Journal of Gastroenterology and Hepatology*, Vol 3, No 12, 1991, pp883-91
43. Ledward, op cit, pp148-65
44. Lynch, et al, op cit, pp1365-8
45. Ledward, op cit, p155
46. Lynch, et al, op cit, pp1365-8
47. Rubin, op cit, p38
48. Ledward, op cit, pp148-65
49. Collignon, P., Heihir, J. and Mitchell, D., "Successful treatment of falciparum malaria in pregnancy with mefloquine", *Lancet*, No 8644, 29 Apr 1989, p967
50. Anon., *The Prescriber*, op cit, p8
51. Hawkins, op cit, pp100-1 and 105
52. Chetley, A., *Peddling Placebos: an analysis of cough and cold remedies*, Amsterdam, HAI, 1989
53. *MIMS Africa*, Vol 31, No 4, July 1991, p111; *MIMS Caribbean*, Vol 21, No 1, Jan 1991, p62
54. Loudon, J.B., "Psychotropic drugs", in: Rubin, op cit, pp49-57
55. Palmer, P.G., "Sedatives and anticonvulsants in pregnancy", in: Hawkins, op cit, pp128-147
56. Niebyl, op cit, pp375-88
57. Palmer, op cit, pp128-147
58. Anon., *The Prescriber*, op cit, p10
59. AMA, op cit, p90
60. Palmer, op cit, pp128-147
61. Sidhu, R.K., "Corticosteroids in pregnancy" in: Hawkins, op cit, pp166-79
62. Anon., "Asthma, progesterone, and pregnancy", *Lancet*, Vol 335, 27 Jan 1990, p204
63. Jones, K.L., Lacro, R.V., et al, "Pattern of malformations in the children of women treated with carbamazepine during pregnancy", *New England Journal of Medicine*, Vol 320, No 25, 22 June 1989, pp1661-6
64. Brodie, M.J., "Management of epilepsy during pregnancy and lactation", *Lancet*, Vol 336, 18 Aug 1990, pp426-7
65. Anon., "Teratogenesis with carbamazepine", *Lancet*, Vol 337, 1 Jun 1991, pp1316-17
66. Piacquadio, K., Hollingsworth, D.R. and Murphy, H., "Effects of in-utero exposure to oral hypoglycaemic drugs", *Lancet*, Vol 338, 5 Oct 1991, pp866-9
67. Hawkins, op cit, pp100-1 and 105
68. Phillips, A., Rakusen, J. (eds) and the Boston Women's Health Collective, *The New Our Bodies, Ourselves* (2nd UK edition), London, Penguin Books, 1989, p347
69. Howden, op cit, pp19-25
70. Jackson, D.M. and Soothill, R., *Is the Medicine Making You Ill?*, North Ryde, Australia, Angus & Robertson, 1989, p100
71. Howden, op cit, pp19-25
72. BMA and the Royal Pharmaceutical Society of Great Britain, op cit, p162
73. Hawkins, op cit, p105
74. Anon., "FDA tightens warning on ACE-inhibitors", *Scrip*, No 1702, 20 Mar 1992, p20
75. Weber, J.C.P., "Limitations of a voluntary reporting system", in: Hawkins, op cit, pp37-47
76. Henry, op cit, p409
77. Phillips, and Rakusen, op cit, p347
78. Hawkins, op cit, p67
79. AMA, op cit, pp843-4
80. Hawkins, op cit, pp64-6
81. Anon., "Preventing iron-deficiency anaemia", *Lancet*, No 8673, 18 Nov 1989, p1231
82. Ramalingaswami, V., "Challenges and opportunities – one vitamin, two minerals", *World Health Forum*, Vol 13, No 2/3, 1992, pp222-31
83. Larroque, B., Kaminski, M., et al, "Folate status during pregnancy: relationship with alcohol consumption, other maternal risk factors and pregnancy outcome", *European Journal of Obstetrics and Gynecology and Reproductive Biology*, Vol 43, 1992, pp19-27
84. Hobbins, J.C., "Diagnosis and management of neural-tube defects today", *New England Journal of Medicine*, Vol 324, No 10, 7 Mar 1991, pp690-1
85. Anon., "UK folic acid supplementation", *Lancet*, Vol 341, 2 Jan 1993, p46
86. Gilman, et al, op cit, p1290
87. AMA, op cit, p701
88. WHO, *Drugs in Pregnancy and Delivery*, Copenhagen, Dec 1984, p53
89. Cody, P., "A history of the DES action movement", in: Mintzes, B. (ed.), *DES: A Drug with Consequences for Current Health Policy*, Utrecht, DES Action The Netherlands, 1990, pp10-12
90. Gilman, et al, op cit, p1401
91. AMA, op cit, p727
92. BMA and the Royal Pharmaceutical Society of Great Britain, op cit, p499

Chetley, A. *Problem Drugs*, Amsterdam, Health Action International, 1993

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The time bomb explodes

"Take a brand new drug. Then, based primarily on theory, manufacture it and prescribe it to millions of patients for over 30 years. Stop only when it is shown beyond doubt to cause cancer."[1]

With those three sentences, Cynthia Laitman,[2] a mother who took the drug in question – DES (diethylstilbestrol) – describes a product that has been called everything from "a medical nightmare"[3] to a "toxic time bomb".[4] The "nightmare" was the range of side effects that have been found in daughters, sons and mothers exposed to DES during pregnancy. The "time bomb" refers to the long gestation period for these effects to emerge, and the indications that the effects may even stretch into a third generation.

DES is a synthetic oestrogen, first developed by Sir Edward Charles Dodds in 1938. Three times more potent than the natural oestrogen, oestradiol, DES was soluble in water and effective when taken orally, whereas the natural hormone had to be injected. Because DES was never patented, in no time at all several manufacturers had the drug on the market. In the USA alone, 267 pharmaceutical companies were eventually granted licences to manufacture and sell DES.[5] Table 7B-1, on page 140, gives an indication of some of the brand names under which DES and related oestrogens have been sold around the world.

No one was sure what DES could be used for. It was tried in many clinical conditions including amenorrhoea (absence of menstrual bleeding), dysmenorrhoea (painful menstruation), senile vaginitis and the suppression of unwanted lactation. However, a leading use for DES soon became the prevention of miscarriage. This use was widely accepted, not on the basis of therapeutic evaluation, but on the strength of what the World Health Organization (WHO) calls "an assertive deduction".[6] The main impetus for this came from research carried out by Drs George and Olive Smith between 1938 and 1948. They were working on the theory that habitual abortion was caused by a lack of progesterone and that giving oestrogen would stimulate the production of progesterone. On the basis of a poorly designed trial of 632 pregnant women, the Smiths claimed in a 1948 article in the *American Journal of Obstetrics and Gynecology* that administering DES could increase the chance of a successful pregnancy in women who had had previous miscarriages or suffered from high blood pressure, and that the risk of premature deliveries would be reduced.[7]

Between 1948 and 1971, DES was given to some two to three million pregnant women in the USA alone, thereby exposing between two to three million of their children to the effects of the drug.[8] The Canadian health authority estimates that some 400,000 children could have been exposed.[9] In Europe an estimated four million women may have used DES while pregnant.[10] In the Netherlands, between 180,000 and 380,000 women were treated with DES while pregnant. In France, an estimated 200,000 pregnant women and their children were exposed to DES.[11]

Extravagant promotion of the drug helped ensure its widespread use throughout North America, Europe, Latin America, Africa, the Middle East and Asia. For example, a 1957 advertisement in the *American Journal of Obstetrics and Gynecology* by the Grant Chemical Company claimed its DesPlex brand was able "to prevent abortion, miscarriage and premature labor" and recommended the drug "for routine

prophylaxis in ALL pregnancies" with "no gastric or other side effects".

Ineffective and unsafe

However, DES was ineffective. A double blind, placebo controlled study of 1,600 women published in 1953 showed clearly that DES did not reduce the incidence of abortion, prematurity or postmaturity.[12] Sadly, the study failed to report the important point that DES "significantly increased abortions, neonatal deaths and premature births"[13] – a conclusion that could, and should, have been made from the data in the study.

Not only was DES ineffective, but it was also unsafe. In the late 1930s and early 1940s, animal research showed that DES and other oestrogens could cause cancer.[14] The link between the use of DES and the development of cancer in humans was made in 1971. Researchers found a rare form of vaginal and cervical cancer (clear cell adenocarcinoma) in daughters of women who had taken DES early in pregnancy. The US Food and Drug Administration (FDA) quickly withdrew approval for DES use in pregnancy.[15]

Other countries reacted more slowly. Austria withdrew all products containing diethylstilbestrol, dienestrol, hexestrol and their derivatives in 1977; Italy withdrew diethylstilbestrol; and in 1980, Kuwait banned the import of products containing DES or diethylstilbestrol diphosphate. Germany and Greece have restricted the indication for use of DES to the treatment of prostate cancer; Saudi Arabia and Tunisia have prohibited the use of DES in pregnancy.[16] France banned the use of DES in pregnancy in 1977. The Netherlands made the decision to ban use in pregnancy in 1972, although it took another three years before the ban was put into effect and the indication "for use in cases of risk of miscarriage" disappeared off the label.[17]

Most of us who are DES-exposed can remember exactly when we first learned about DES. I was reading my morning paper one April day in 1971 when I saw the headline `Drug Passes Rare Cancer to Daughters'. The minute I read the story I was clutched with fear. There was no doubt this was me; I remembered well taking those little pills four times a day for seven months during my pregnancy."

– Pat Cody, co-founder of DES Action USA

Fortunately, clear cell adenocarcinoma is rare, occurring in only one in 1,000 to one in 10,000 exposed daughters.[18] But it mainly affects women in their early twenties and it is not a cancer that was previously seen in women of this age. As a result, it has been described as "fundamentally a new iatrogenic (medically induced) disease".[19] The treatment involves extensive and mutilating surgery or radiation therapy.

In addition, DES daughters are about twice as likely as unexposed women to develop pre-cancerous abnormalities of the cervix and vagina and carcinoma in situ.[20]

In addition, DES daughters are about twice as likely as unexposed women to develop pre-cancerous abnormalities of the cervix and vagina and carcinoma in situ.[20]

At least two-thirds of DES daughters have adenosis, a condition in which mucus-producing cells normally found inside the cervical canal are also present on the surface of the cervix and vagina. Adenosis can cause a more abundant vaginal discharge. This condition is harmless, naturally regresses over time, and does not require any medical treatment. Structural defects of the cervix, vagina, uterus and fallopian tubes have been found in more than 40% of DES daughters,[21] with one study putting the figure at two-thirds of exposed daughters.[22] DES daughters are more likely to be infertile than other women. Further, DES daughters have a much increased risk of a number of adverse pregnancy outcomes. Compared with non-exposed women, DES daughters have four times the risk of miscarriage and pre-term labour.[23] Ectopic pregnancy – which can be a life-threatening condition – occurs in 4-8% of pregnancies in DES daughters.[24]

All DES daughters need special gynaecological examinations annually. They should be performed by a

The October 1988 listing for Ethica's Stilboestrol in the *Indonesia Index of Medical Specialities* includes "inhibition of lactation" as one of the indications for the drug. Another indication is "amenorrhoea". Pregnancy is the most common cause of amenorrhoea.

In December 1990 in *MIMS Middle East* and July 1991 in *MIMS Africa* the listing for Norgine's Tampovagan (stilboestrol) indicates the product for vaginal irritation including if it is caused by the menopause, a common and minor health complaint for which a form of DES should *not* be used. The *British National Formulary* describes Tampovagan as "less suitable for prescribing".[36]

The use of DES or other oestrogens as a "morning-after" pill has risks for the fetus if the woman is pregnant and the pill does not work. The *Physicians' Desk Reference* in the USA carries the clear message, approved by the US FDA, that DES "should not be used as a postcoital contraceptive".[37]

Even the use of oestrogens such as DES in the palliative treatment of breast and prostate cancers (the only indications for DES in the UK or in the USA) is being questioned. The British Medical Association notes that "side effects are common with the drug, and it is because of these potential risks that it is now less widely used."[38]

No matter what the indication for the product, in many developing countries, products containing DES are available without a prescription, not just over the counter, but in street markets. The mere availability of the product prolongs the unnecessary risk to women and their children.

DES in animals

Another use for DES and related oestrogens has been in animals as growth stimulants. Unlike natural steroids, they are not readily destroyed in the liver and residues remain in meat products. According to WHO,

> "the continuing accumulation of evidence that diethylstilbestrol is a potential carcinogen in man and the discovery of undesirably high levels of diethylstilbestrol in some baby foods within the past few years, provides strong endorsement of the decision already taken in many countries to ban the use of all stilbenes as growth promoting agents."[39]

DES has been banned for both human and veterinary use in the Philippines.[40] The European Community adopted a directive in 1981 which banned the use of DES and other stilbenes in animals.[41] Originally banned for use in animals in the USA in 1972, an appeal court decision overturned the ban in 1974 and it was not until 1979 that the US FDA again banned the use of the drug as a growth promoter in cattle and sheep.[42] However, as late as February 1983, 1,500 cattle were found on several farms with recent residues of DES in their system because of illegal use.[43]

"Risk without benefit"

Although DES was originally prescribed with the hope of benefitting women who might have difficult pregnancies, as one obstetrician/ gynaecologist puts it, "DES presented risk without benefit".[44] There can no longer be any excuse for extending that risk.

Lawsuits seek compensation

More than 1,000 lawsuits have been filed in the USA in an attempt to gain compensation for the victims of DES. Because of the large number of manufacturers and the time lag between taking the drug and its effects becoming evident, it has often been difficult for women to identify the precise brand of DES that they or their mothers took. This meant that in many of the early cases, the women were not able to identify the individual manufacturer, and therefore lost. In 1980, however, the California Supreme Court ruled that women should be able to sue the companies as a group and that if the suit was successful, companies should pay compensation according to the market share each company had at the time the drug was used. Other legal arguments have been accepted by different courts in the USA, including alternative liability, concert of action, enterprise liability, and risk contribution.

The Dutch Supreme Court took a different approach in a case brought by six DES daughters against the 10 companies known to have sold DES in the Netherlands. The case began in 1986 and the district court and appeal court both found against the daughters on the grounds that they were unable to cite the company that produced the DES pills that their mothers had taken. The Supreme Court decided in October 1992 that such a burden of proof was unacceptable, and ruled that every manufacturer should be equally and fully liable for damages, regardless of their market share at the time. This decision has opened the door for the case to return to the appeal court to be judged on grounds of negligence, foreseeability and causation.

Sources: Anon., "Diethylstilboestrol – effects of exposure in utero", *Drug and Therapeutics Bulletin*, Vol 29, No 13, 24 Jun 1991, pp49-50; Cody, P., "A history of the DES action movement", in: Mintzes, B. (ed.), *DES: A Drug with Consequences for Current Health Policy*, Utrecht, DES Action The Netherlands, 1990, pp10-12; Dutton, D.B., *Worse than the disease. pitfalls of medical progress*, New York, Cambridge University Press, 1988, p262-5; Spanjer, M., "Netherlands: Liability for diethylstilboestrol damage", *Lancet*, Vol 340, 21 Nov 1992, p1280

gynaecologist who is familiar with DES-related problems. Being a DES daughter may have implications for contraceptive choices, treatment with fertility drugs, and pregnancy. Some doctors advise great caution with the use of fertility-related drugs and hormonal contraceptives.[25]

It is not only DES daughters who are affected. Effects on sons whose mothers used DES are not as clear. This is mainly due to a lack of studies. One relatively large study found no excess of urogenital anomalies in exposed sons;[26] however, other studies found an increase in epididymal and testicular abnormalities such as undescended testes, incomplete or defective testicular development and low sperm counts.[27]

Mothers who took DES have a 1.5 times increased risk of breast cancer and there is concern that an increased risk of breast cancer may also emerge among their daughters.[28]

According to one professor of obstetrics and gynaecology,

> "This whole thing could be a time bomb. I hesitate to use that word, but effects keep popping up. First it was in the female in the cervix, then in the female in the uterus and the male in the Wolffian ducts, and who knows in the future what may be in store."[29]

Other uses?

Goodman and Gilman's textbook on pharmacology leaves no doubt: "the use of estrogens in pregnancy is not indicated". It makes the point that "pregnant patients should not be given estrogens, particularly during the first trimester – a time when the fetal reproductive tract is developing and may be influenced by exogenous estrogens".[30] Similarly, the American Medical Association (AMA) is crystal clear on this point:

> "The administration of any estrogen is contraindicated during pregnancy. The use of synthetic hormones to treat threatened abortion is ineffective and carries the risk of teratogenicity."[31]

However, oestrogens, including DES, remain in use for other indications such as suppression of lactation, menopausal problems, as a postcoital (morning-after) pill, and as therapy for some breast and prostate cancer. There are dangers associated with these uses. DES, as a known carcinogen, should not be used as a morning after pill, lactation suppressant or for menopause. There are also better alternatives for breast and prostate cancer.

Goodman and Gilman note that the use of oestrogens to relieve breast engorgement or suppress lactation after delivery "has decreased in recent years, since the incidence of painful engorgement is

DES Action groups

In 1974 Pat Cody, an American woman who had taken DES during pregnancy, wrote to the national Department of Health to ask what was being done to notify the millions of women who had taken DES. "We're doing a study," the Department of Health responded. "We don't want to alarm women." Harriet Simand, a Canadian who became aware of her DES exposure when she developed cancer, was told that "DES wasn't really a problem in Canada, only in the US", when she tried to find out what had been done to notify DES-exposed people in Canada.

Anita Direcks from the Netherlands spoke in 1990 about the continued lack of information and resources for DES-exposed people in Europe, "In most European countries, the national governments, the medical profession, and the general public seem to be hardly aware of the DES-problem in their countries. The national authorities have forbidden the use of DES during pregnancy, but have not informed the medical profession nor the public of the consequences of exposure to DES."

In response to the view that DES is a mistake of the past – best forgotten – exposed women have formed DES Action groups in the USA in 1975, Australia in 1980, the Netherlands in 1981, Canada in 1982, France in 1987, the UK in 1989, Ireland in 1990 and a European network in 1988. In Italy and Germany, women's health organisations initiated national campaigns on DES in 1988. Networks of women with cancer from DES exposure have also been formed in the US, the Netherlands and in Europe.

DES Action groups raise public awareness about DES in order to reach and inform people who are as yet unaware of their exposure. They provide information and counselling for DES-exposed people and information for the medical profession on appropriate health care. They also provide support for litigation and act as political pressure groups to ensure that the problem of DES exposure is taken seriously by national authorities and the medical profession.

Source: Mintzes, B. (ed.), *DES: A Drug with Consequences for Current Health Policy*, Utrecht, DES Action The Netherlands, 1990, pp8, 10 and 31

low and this condition is readily controlled with analgesics."[32] According to the AMA, oestrogens "have been used to prevent postpartum lactation.... However, there is an increased risk of thromboembolic phenomena [blood clots], and rebound lactation often occurs after withdrawal of medication." As a result, other drugs are now recommended in the rare instances when it might be necessary to suppress lactation with drug therapy.[33] "Physical methods of lactation suppression, like breast binding, are associated with more pain in the first week after delivery than pharmacological methods, but they appear to be more effective in the longer term."[34] The US FDA withdrew the indication of suppression of lactation for oestrogens in 1978.[35]

Table 7B-1
Names under which DES and related oestrogens have been sold

Acestrol
Acro-Estrol
Agostilben
Agostilgen
Albestrol
Amperone
Antigestil

Benzestrol
Bio-des
Bufon

Calmovarin
Carnostrol
Chembestrol
Chlorotrianisene
Cicloestrina
Climazin
Climoterine
Clinestrol
Clinoestrol
Comestrol
Cyren
Cyren A
Cyren B

DAES
Dawe's Destrol
Deb
Delvinal
DES
Desma
DesPlex
Destrol
Diastyl
Diathylstilbostrol Dibestil
Dibestrol 2 Premix
Dicorvin
Dienestrol
Dienoestrol
Di-erone
Diestryl
Diethylex
Diethylstilbenediol
Diethylstilbestrol
Dietilstilbestrol Digestil
Discorvin
Distilbene
Domestrol
Dyestrol

Enboestrol
Estilbestrol
Estilben
Estilbin
Estilbin MCO
Estimon
Estril
Estrobene
Estrofix
Estromenin
Estromon
Estrosyn
Estrovena

Follidien
Fonatol

Ginoxol
Grafestrol
Gynben
Gyneben
Gynestogene
Gynopharm

H-Bestrol
Hexestrol
Hexoestrol
Hi-Bestrol
Holzinger
Honvol
Hormostilboral

Idroestril
Implanetten
Implantin
Iscovesco

Laboestrin
Linguets

Makarol
Manostilbeen
Menocrin
Menosteroid
Menostilbeen
Meprane
Mestilbol
Mestralon
Methallenestrol
Metrokin
Metysil
Micrest
Microest
Microsest
Mikarol
Milestrol
Monomestrol

Neo-Foliculanpomada
Neo Oestranol
New-Estanol
Nomestrol
Normavagin
Normestrol
Novostilbestrol
Novostilboestrol NSC-3070
Nulabort
Oekolp
Oestrodienolum
Oestrogen-Holzinger
Oestrogenin
Oestrogenine
Oestrol Vetag
Oestromenin
Oestromensyl
Oestromon
Opoginol
Orestol
Ostromenin
Ovendosyn
Ovextrol

Pabalate
Pabestrol
Palestrol
Palmestil
Percutacrine
  Oestrogenique
  Isocovesco
Phenestrol
Preostrin(a)
Protectona

Ragestrol
Remrumestrol 2
Restrol
Rumestrol 1
Rumestrol 2
Rymestrol

Sedestran
Serral
Sexestrol
Sexocretin
Sexogen
Sibol
Sintestrol
Stibilium
Stibrol
Stil
Stilbal
Stilbarol
Stilbenol
Stilbest-Oral
Stilbestrina
Stilbestrol
Stilbestronate
Stilbestrone
Stilbestrosan
Stilbetan C
Stilbetin
Stilbilium
Stilbindon
Stilbinol
Stilboefral
Stilboestroform
Stilboestrol
Stilbofollin
Stilbol(um)
Stilboral
Stilbostrol
Stilcap
Stilestrate
Stilkap
Stilnestrin
Stilpalmitate
Stilphostrol
Stilrol
Stilronate
Stilrone
Stils
Synestrin
Synestrol
Synoestrin
Synthoerin
Synthoestrin
Synthofollin
Syntofollin

Tace
Tampovagan
Tylandril
Tylosterone

Vagestrol
Vallestril

Willestrol

Sources: United Nations, *Consolidated List of Products Whose Consumption and/or Sale Have Been Banned, Withdrawn, Severely Restricted or Not Approved by Governments*, 2nd issue, Doc No ST/ESA/192, New York, 1987, pp312-3; Wemos/HAI International Group on Women and Pharmaceuticals, "D.E.S.", *Women and Pharmaceuticals* (pack), Amsterdam, 1987, p4; Hardon, A. (ed.), *Women and Pharmaceuticals Bulletin*, Amsterdam, Wemos/HAI International Group on Women and Pharmaceuticals, Nov 1990, p6; DES Action Canada, *DES: The Wonder Drug You Should Wonder About*, Montreal, no date; Somers, D.C, *Diethylstilboestrol au Bresil*, unpub. thesis, Universite Pierre et Marie Curie, Paris, 1993, p58

Recommendations for action

1. DES should be banned both as a product for humans and for use as growth stimulants in animals raised for human consumption.
2. Governments should research the extent of the problem and, where possible, attempt to trace all DES-exposed people and provide them with full, accurate information on the problems they could face, and make appropriate health care available.
3. Health workers should be informed on how to recognise the signs of DES exposure and monitor and treat associated health problems.
4. Universities and health workers should undertake further research into the effects that DES may have on DES mothers, their children, and their children's children (the so-called third generation).

Notes and references:

1. Laitman, C., "DES on prescription: it's time for Europe to act", *Scientific European*, Oct 1990, pp27-9
2. Cynthia Laitman is a biologist and writer and is the author of one of the first books on DES – *DES: the complete story*, New York, St Martin's Press, 1981.
3. Brackbill, Y. and Berendes, H.W., "Dangers of diethylstilboestrol: Review of a 1953 paper", *Lancet*, 2 Sept 1978
4. Anon., "Diethylstilboestrol – effects of exposure in utero", *Drug and Therapeutics Bulletin*, Vol 29, No 13, 24 Jun 1991, pp49-50
5. Laitman, op cit
6. WHO, *Drug Information*, Doc No PDT/DI/84 4, Geneva, Oct-Dec 1984, pp8-10
7. Smith, O.W., "Diethylstilbestrol in the prevention and treatment of complications of pregnancy", *American Journal of Obstetrics and Gynecology*, Vol 56, 1948, pp821-34
8. Stillman, R.J., "In utero exposure to diethylstilbestrol: adverse effects on the reproductive tract and reproductive performance in male and female offspring", *American Journal of Obstetrics and Gynecology*, Vol 142, No 7, 1 Apr 1982, pp905-21
9. Martin, L., "The DES issue", *Protect Yourself*, Sep 1983, pp42-4
10. Cody, P., "A history of the DES action movement", in: Mintzes, B. (ed.), *DES: A Drug with Consequences for Current Health Policy*, Utrecht, DES Action The Netherlands, 1990, pp10-12
11. von Eickstedt, K.-W., "Sex hormones and related compounds including hormonal contraceptives", in: Dukes, M.N.G. and Beeley, L., (eds), *Side Effects of Drugs Annual 14*, Amsterdam, Elsevier, 1990, pp343-64
12. Dickmann, W.J., Davis, M.E., et al, "Does the administration of diethylstilbestrol during pregnancy have therapeutic value?", *American Journal of Obstetrics and Gynecology*, Vol 66, 1953, pp1062-81
13. Brackbill and Berendes, op cit
14. Geschickter, C.T., "Mammary carcinoma in rat with metastasis induced by estrogen", *Science*, Vol 89, 1939, p35; Shimkin, M.B., Grady, H.G., "Carcinogenic potency of stilbestrol and estrone in strain C3H mice", *Journal of the National Cancer Institutes*, Vol 1, 1940, p19
15. 't Hoen, E., "Diethylstilbestrol, the effects on the health of users and their children", in: Hardon, A. (ed.), *Women and Pharmaceuticals Bulletin*, Amsterdam, Wemos/HAI International Group on Women and Pharmaceuticals, Nov 1990, pp5-7
16. United Nations, *Consolidated List of Products Whose Consumption and/or Sale Have Been Banned, Withdrawn, Severely Restricted or Not Approved by Governments*, 2nd issue, Doc No ST/ESA/192, New York, 1987, p38
17. Direcks, A. and 't Hoen, E., "DES: the crime continues" in McDonnell, K. (ed.), *Adverse Effects: Women and the Pharmaceutical Industry*, Penang, IOCU, 1986, pp41-9
18. Anon., "Diethylstilboestrol – effects of exposure in utero", *Drug and Therapeutics Bulletin*, Vol 29, No 13, 24 Jun 1991, pp49-50
19. Rakusen, J., "DES", in: Phillips, A., Rakusen, J. (eds) and the Boston Women's Health Collective, *The New Our Bodies, Ourselves* (2nd UK edition), London, Penguin Books, 1989, p520
20. AMA, *Drug Evaluations*, Philadelphia, W.B. Saunders Co., (6th edn) 1986, p701
21. Anon., *Drug and Therapeutics Bulletin*, op cit, pp49-50
22. AMA, op cit, p701
23. Senekjian, E.K., Potkul, R.K., et al, "Infertility among daughters either exposed or not-exposed to diethylbesterol", *American Journal of Obstetrics and Gynecology*, Vol 158, 1988, pp493-8; Barnes, A.B., Colton, T., et al, "Fertility and outcome of pregnancy in women exposed in utero to diethylstilbestrol", *New England Journal of Medicine*, Vol 302, 1980, pp609-13; Stillman, op cit
24. Kleiverda, G., "How can we provide appropriate care for DES-exposed women?", in: Mintzes, op cit, pp14-18
25. Ibid
26. Leary, F.J., Resseguie, L.J., et al, "Males exposed in utero to diethylstilbestrol", *Journal of the American Medical Association*, Vol 252, 1984, pp2984-9
27. Gill, W.B., Schumacher, G.F.B., et al, "Assocation with diethylstilbestrol exposure in utero with cryptorchidism, testicularhypoplasma and semen abnormalities", *Journal of Urology*, Vol 122, 1979, pp36-9; Gill, W.B., Schumacher, G.F.B., et al, "Male genital tract changes in humans following intrauterine exposure to diethylstilbestrol", in: Herbst, A.L. and Bern, H.A. (eds), *Developmental Effects of Diethylstilbestrol (DES) in Pregnancy*, New York, Thieme Stratton, 1981, pp103-19
28. Anon., *Drug and Therapeutics Bulletin*, op cit
29. Anon., "Odd-shaped uteri mark daughters of DES women", *Medical Tribune*, 19 July 1977
30. Gilman, A.G., Rall, T.W., Nies, A.S., and Taylor, P., *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, New York, Pergamon Press, (8th edn) 1990, pp1390 and 1393
31. AMA, op cit, p701
32. Gilman, et al, op cit, p1395
33. AMA, op cit, p699
34. Enkin, M., Keirse, M. and Chalmers, I., *A Guide to Effective Care in Pregnancy and Childbirth*, Oxford, Oxford University Press, 1989, p336
35. DES Task Force, *Summary Report*, DHEW Pub No (NIH) 79-1688, Washington, Dept of Health, Education and Welfare, 21 Sep 1978, p14
36. BMA and the Royal Pharmaceutical Society of Great Britain, *British National Formulary*, London, BMA and The Pharmaceutical Press, No 23, Mar 1992, p280
37. *Physicians' Desk Reference*, Oradell, NJ, Medical Economics Company, 44th edn, 1990, p1211
38. Henry, J. (ed.), *The British Medical Association Guide to Medicines & Drugs*, London, Dorling Kindersley, (2nd edn) 1991, p373
39. WHO, op cit
40. Tan, M.L., *Dying for Drugs: Pill power and politics in the Philippines*, Manila, Health Action Information Network, 1988, p106
41. Jopling, M., "The growth factor", *The Guardian*, 29 July 1986
42. Anon., "FDA bans DES in animals", *The Nation's Health*, Aug 1979
43. Schell, O., *Modern Meat*, New York, Random House, 1984, pp253-4
44. Stillman, op cit

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A sordid, sorry tale

Salma suspected she was pregnant again. Her husband suggested that she go to a nearby maternity clinic in Karachi, Pakistan. The doctor prescribed a course of oestrogen-progesterone (EP) tablets to test pregnancy and told her to come back after five days. When she did, he confirmed that she was pregnant. Months later, she woke up in the middle of the night in pain and was rushed to the maternity home. She gave birth to a baby girl – born without eyes.[1]

Mercy, a Filipino woman, also suspected that she was pregnant. She went to her doctor who gave her an injection of Gynaecosid, an EP drug. She went back two more times, and each time he gave another injection. After the third visit, the doctor confirmed that Mercy was pregnant. She later gave birth to a boy with a club foot.[2]

The use of high-dose EP drugs – those that contain about 0.05 milligrams of oestrogen and 10 milligrams or more of progestogen – to test for pregnancy has been popular in many developing countries. It is a deceptively simple procedure. High-dose EP drugs were originally introduced in the 1950s to help regulate menstrual disorders, as they were thought to start menstruation in women whose periods were delayed and who were not pregnant. Thus, a woman whose period did not start after taking EP drugs was assumed to be pregnant. The problem is that high-dose EP drugs are both unreliable and unsafe as pregnancy tests. A study published in the *International Journal of Gynaecology and Obstetrics* in 1976 indicated that the test result was false positive in about one out of every five women.[3]

The identification of harmful effects on the fetus came in 1967 in a study by Dr Isabel Gal and her colleagues.[4] For the next 10 years, a regular flow of papers appeared reporting on the dangers of these drugs.[5] Abortions, stillbirths, malformed live births and possible long-delayed effects (such as the risk of cancer in children) are among the dangers of giving high doses of sex hormones at an early stage of fetal development.

These findings led some governments to ban the use of high-dose EP drugs entirely, or prevent their use for pregnancy testing. They were withdrawn in Norway and Sweden in 1970; Finland in 1971; Denmark in 1974; the USA and Australia in 1975; the UK in 1977; Austria, Belgium and Italy in 1978; Greece in 1980. They were banned for import into Singapore in 1978, withdrawn in New Zealand, prohibited in Thailand, not approved for use or sale in Venezuela, not allowed to be promoted for pregnancy testing in South Africa, and are not recommended for use in Saudi Arabia. In Germany, high-dose EP drugs were withdrawn for the indication of use as treatment in secondary amenorrhoea (absence of menstrual periods).[6]

In the USA, the Food and Drug Administration said the products had been withdrawn for use in pregnancy testing because there was "a lack of proof of safety for that use in view of the potential danger in the presence of pregnancy and the availability of accurate alternatives".[7] It took the position that

there was "no justification for using progestogen and estrogen in threatened abortion or as a pregnancy test".[8] The American Medical Association describes hormonal pregnancy tests as "outmoded".[9]

In 1981, the World Health Organization (WHO) recommended an end to the use of high-dose EP drugs during pregnancy. WHO said that as a pregnancy test, the products were unreliable and there was no way of guaranteeing that they would not harm the fetus. Besides, a safer alternative – the urine test – was on the market.[10]

An easy abortion?

Another part of the mythology of high-dose EP drugs is the belief that they can be used to induce abortion, even though none of the companies have promoted the products for this purpose. An acknowledged side effect of high-dose EP drugs is spontaneous abortion. As many as one in 10 women who used high-dose EP drugs to test for pregnancy were found to have had a spontaneous abortion.[11] Unfortunately, many women have been led to misuse this "side effect" to induce abortion – with tragic results when the method fails, which it often does. In one study of 52 mothers in Madras, India who had given birth to babies with congenital defects, 31% had taken hormonal preparations during early pregnancy, often with a view to termination.[12]

By the early 1980s, research in countries such as India, Peru, Chile and the Philippines was demonstrating that the use of EP drugs to cause an abortion was a growing trend.[13] One researcher in Peru commented,

> "One of the most alarming examples of dangerous drug use I encountered is that of injections (mainly oestrogen-progesterone combinations) in the mistaken belief that they will terminate unwanted pregnancies. From observations in drug stores, discussions with health workers and a series of interviews conducted in some of the poorest districts of the Peruvian city of Chimbote – I got the impression that their use is widespread in poor communities in Latin America."[14]

In India, researchers claimed in 1980 that high-dose EP drugs were being used with "the intention of inducing abortion" – successfully in some cases. They commented, "these hormones are easily available for patients seeking abortions with no restrictions".[15]

Menstrual disorders

High-dose EP drugs are still used as a treatment for menstrual disorders, but even this is a very doubtful indication. WHO pointed out in 1981 that it was

Removing high-dose EP drugs in India

In June 1982, on the advice of the Indian Council for Medical Research, the Drug Controller of India issued a notice to ban all high-dose EP drugs, with production to cease from the end of 1982 and sales to end from the end of June 1983. Very quickly, three companies – Unichem, Nicholas and Organon – filed suits in the Bombay and Calcutta courts arguing for a stay order until a legal decision was handed down. The Federation of Associations of Obstetricians and Gynaecologists and the Organisation of Pharmaceutical Producers of India also raised their voices in opposition to the ban.

In January 1983, a stay order was granted against the ban and two-year extensions of product licences were granted by the courts. The stay order was further extended while the Supreme Court deliberated the matter. Finally in November 1986, the Court directed the Drug Controller to hold public hearings on whether *all* oestrogen-progesterone products, including low-dose oral contraceptives, would remain on the market. This extension of the discussion to products that were clearly of use served only to complicate the issue.

Four public hearings were held – in Madras, Delhi, Calcutta and Bombay – although the notices announcing the hearings came late and were not widely publicised. This made it difficult for bodies such as the Voluntary Health Association of India and the All Indian Drug Action Network – both of which were campaigning strongly to have the drugs removed – to prepare for the hearings. Nonetheless, they were able to present considerable evidence from around the world to demonstrate that there was no need for these drugs. During the hearings, the main industry argument was that unquestionably, the products should not be used in pregnancy, but that they were of use to treat gynaecological conditions in non-pregnant women. The industry argued that if abuse of the products occurred – that is, if they were taken by pregnant women – the industry could not be held responsible for that, nor should it be penalised by not being allowed to sell a supposedly useful product. Clinical pharmacologist Professor Michael Rawlins, of Newcastle University in the UK, said quite bluntly in evidence presented to the hearings that he was "dismayed that the Indian pharmaceutical industry should wish to seek to maintain their market in high-dose oestrogen-progestogen products".

In the end, nearly one year after the final public hearing, on 15 June 1988, the Drug Controller announced that the ban on high-dose EP drugs was to go into effect.

Source: Silverman, M., Lydecker, M. and Lee, P.R., *Bad Medicine: the prescription drug industry in the Third World*, Stanford, Stanford University Press, 1992, pp110-24

unwise to use these products as a treatment for missed periods: "Women who are not pregnant will have their menses further delayed if hormones are administered."[16]

According to Dr Stephen Franks, a senior lecturer in reproductive endocrinology at St Mary's Hospital Medical School in London, "there is no justification for the use of these drugs in amenorrhoea, menstrual irregularities and other gynaecological disorders".[17]

Aside from pregnancy, the causes of amenorrhoea can include menopause, breastfeeding, too little body fat, malnutrition, dieting, heavy athletic training, previous use of hormonal contraceptives, stress, hormonal imbalance, congenital defects, tumours, or disease.[18] The specific cause should first be identified and attempts made to treat that cause. It is unlikely that hormonal therapy will be necessary; if it is, then low-dose hormones are preferred.[19] In developing countries, undernutrition or underlying disease conditions are among the most likely causes of secondary amenorrhoea.

Time for action

The dangers of high-dose EP drugs have been known for more than 25 years. Yet, the withdrawal of these products has been painfully slow. Virtually all the sales of high-dose EP drugs now occur in developing countries where the products have not been banned. Warnings about the dangers associated with these drugs are often inadequate or non-existent. A Pakistani publication described the situation as "a sordid, sorry tale of the multinational drugmakers' quest for profit, our doctors' ignorance and the authorities' apathy".[20] A six-year battle in India to have high-dose EP drugs withdrawn further illustrates the reluctance of companies to move quickly (see box on page 144).

During the 1980s, an estimated 180,000 women a year used high-dose EP drugs in India. In the mid-1980s, one in 20 Indian women over the age of 15 used high-dose EP drugs at least once a year. In more than three-quarters of the pharmacies in Cusco, Peru, it was possible to buy high-dose EP drugs without a prescription. Malaysia, Indonesia, Colombia, Brazil and Chile are other countries where widespread use of these drugs has been reported.[21]

In March 1987, the German company, Schering, finally withdrew the world's leading high-dose EP drug, Cumorit, from the global market, following sustained pressure from public interest groups. The Dutch company, Organon, withdrew the oral form of Menstrogen, the second leading product, from the global market in January 1988, again after considerable pressure.[22] (The injectable form is still on the market.)

It is worth putting these withdrawals into some perspective. The first clear warning about the risks of these drugs to the unborn child emerged in 1967. It has taken more than 20 years to get the two leading brands removed globally. This is despite the withdrawal of Menstrogen from the UK market in March 1975, and the withdrawal of the equivalent to Cumorit in the UK in 1978 and in Germany in 1980. Yet there is evidence that similar products are still being used in many countries.

In the Middle East in December 1990, Orion's Divina (2mg oestradiol and 10mg medroxyprogesterone) was indicated for "amenorrhoea", Medimpex's Limovanil (2.5mg oestradiol and 12.5mg progesterone) was indicated for "primary and secondary amenorrhoea... habitual abortion".[23] Also in 1990, in Pakistan, Efroze's Gynaecosid (5mg methyloestrenolone and 0.3mg of methyloestradiol) was recommended for "secondary amenorrhoea"; Organon's Menstrogen (0.02mg ethinylestradiol and 12.5mg progesterone) was indicated for "selected cases of primary and secondary amenorrhoea"; Sami's Penorit (10mg of norethisterone and 0.02mg of ethinyloestradiol) was indicated for "secondary amenorrhoea of short duration".[24]

Part of the problem is the reluctance of companies to face the acknowledged risks of these drugs – risks without any obvious benefits. In 1988, a senior Organon manager, K. Klijn, said that his company's high-dose EP product, Menstrogen injection, offered "no risk for mother or fetus; the product's active principles are natural hormones and no convincing evidence of a teratological or virilizing effect exists".[25]

As long as these drugs remain on the market without adequate warnings or controls on use, thousands of women and their unborn children are exposed to unnecessary danger. As M. D. Rawlins, professor of clinical pharmacology at Newcastle University in the UK, states: "There is no scientific or clinical justification for the continued use of these products."[26]

Recommendations for action

Governments should:

1. ban all high-dose EP drugs, immediately;
2. make available and publicise the use of alternative forms of pregnancy testing;
3. publicise the dangers of taking any drugs during pregnancy.
4. provide access to safe, legal, low-cost abortion to eliminate the demand for abortion through self-medication with hazardous products.

References:

1. Anon., "The untold story", *Herald* (Pakistan), Sept 1982
2. Marcelis, C. and Shiva, M., "EP drugs: unsafe by any name", in: McDonnell, K. (ed.), *Adverse Effects: Women and the Pharmaceutical Industry*, Penang, IOCU, 1986, pp11-26
3. Salam, D.V., et al, "Estrogen-progesterone withdrawal bleeding in diagnosis of early pregnancy", *International Journal of Gynaecology and Obstetrics*, Vol 14, 1976, pp348-53
4. Gal, I., et al, "Hormonal pregnancy tests and congenital malformations", *Nature*, Vol 216, 1967, p83
5. See, for example: Levy, E.P., Cohen, A. and Fraser, F.C., "Hormone treatment during pregnancy and congenital heart defects", *Lancet*, 1973 (I), p611; Janerich, D.T., Piper, J.M. and Glebatis, D.M., "Oral contraceptives and congenital limb-reduction defects", *New England Journal of Medicine*, Vol 291, 1974, pp697-700, Nora, A.H. and Nora, J.J., "A syndrome of multiple congenital anomalies associated with teratogenic exposure", *Archives of Environmental Health*, Vol 30, 1975, pp17-21; Hellstrom, B., Lindsten, J., and Nilsson, K., "Prenatal sex hormone exposure and congenital limb-reduction defects". *Lancet*, 1976 (II), p373; Heinonen, O.P., Slone, D., et al, "Cardiovascular birth defects and antenatal exposure to female sex hormones", *New England Journal of Medicine*, Vol 296, 1977, pp67-70; Janerich, J.T., Dugan, J M., et al, "Congenital heart disease and prenatal exposure to exogenous sex hormones", *British Medical Journal*, 1977, pp1058-60; Nora, J.J., Nora, A.H., et al, "Exogenous progestogen and estrogen implicated in birth defects", *Journal of the American Medical Association*, Vol 240, 1978, pp837-43
6. United Nations, *Consolidated List of Products Whose Consumption and/or Sale Have Been Banned, Withdrawn, Severely Restricted or Not Approved by Governments*, 2nd issue, Doc No ST/ESA/192, New York, 1987, pp111-12; Marcelis and Shiva, op cit, pp11-26; Gal, I., *Teratological Adverse Drug Effects: Review of Evidence Implicating Hormonal Pregnancy Tests*, (mimeo) submitted to UK Department of Health and Social Services, 1978/9, p3
7. United Nations, op cit, pp112
8. Silverman, M., Lydecker, M. and Lee, P.R., *Bad Medicine: the prescription drug industry in the Third World*, Stanford, Stanford University Press, 1992, p112
9. AMA, *Drug Evaluations*, Philadelphia, W.B. Saunders Co., (6th edn) 1986, p700
10. WHO, *The Effect of Female Sex Hormones on fetal Development and Infant Health*, Technical Report Series, No 657, Geneva, 1981
11. Marcelis and Shiva, op cit, pp11-26
12. Voluntary Health Association of India (VHAI), *The Case Against EP Forte*, New Delhi, 1983, p1
13. Wolffers, I., Hardon, A., and Janssen, J., *Marketing Fertility: Women, Menstruation and the Pharmaceutical Industry*, Amsterdam, WEMOS International Group on Women and Pharmaceuticals, 1989, p28
14. Melrose, D., *Report on Research and Networking Visit to Latin America*, The Hague, HAI, 1983, pp9-10
15. Palaniappan, B. and Poorva Devi, V., "Hormones for withdrawal bleeding", *Journal of the Indian Medical Association*, Vol 74, No 4, 18 Feb 1980, p69
16. WHO, op cit
17. Silverman, et al, op cit, p117
18. Phillips, A., Rakusen, J. (eds) and the Boston Women's Health Collective, *The New Our Bodies, Ourselves* (2nd UK edition), London, Penguin Books, 1989, p510
19. Wolffers, et al, op cit, p25
20. Anon., *Herald*, op cit
21. Wolffers, et al, op cit, pp45-50
22. Ibid, pp32 and 44
23. *MIMS Middle East*, Vol 21, No 6, Dec 1990, pp81-2
24. Qureshi, A.H. (ed.), *Quick Index of Medical Preparations*, Vol 22, No 1 and 2, Mar-Aug 1990, pp71-2
25. MaLAM, *Newsletter*, Sep 1988, p1
26. Silverman, et al, op cit, p118

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8A. Contraceptives

Who's in control?

"The burden of ill health associated with reproduction is divided very unequally between the two sexes, with women bearing the brunt of it. For instance, only women face the health hazards of pregnancy and childbirth. Most STDs [sexually transmitted diseases] have more serious sequelae [symptoms or conditions] in women than in men.... Contraceptive use worldwide is three times greater among women than men, and among all available methods, those used by women carry more potential health hazards."[1]

An estimated 381 million people in developing countries use some form of contraception in order to avoid pregnancy.[2] Female sterilisation is the most widely used method in the world, with the intrauterine device (IUD) being the most commonly used *reversible* method.[3] Table 8A-1 gives an indication of the numbers of people using different methods globally, while Figure 8A-1 on page 148 indicates the different patterns of usage globally and in different regions.

Nonetheless, the lack of access to birth control is enormous: "more than 500 million married women now express the desire for access to birth control, but cannot obtain methods suitable to their needs."[4]

Despite the different types of contraception, for most women there is actually a very limited choice. In the words of a 20 year old single woman, "I wish they could find another way.... I feel like you have problems with everything and I don't have very many options except not being sexually active which... I'm not willing to do right now."[5]

The choice is even more limited if a health care provider does not prescribe certain methods or does

Table 8A-1
Global estimates of the number of people using different methods of contraception (1980s)

Method	Number of users
Sterilisation	
male	42 million[1]
female	140 million[1]
Hormonal contraceptives	
oral	63 million[2]
injectables	6 million[3]
implants	1.5 million[4]
IUD	80 million*[5]
Condom	40 million[6]
Other barrier methods	8 million[7]
Natural birth control	32 million[7]
Withdrawal	32 million[7]

*nearly 60 million IUD users are in the People's Republic of China.

Sources:
1. Anon., "Vasectomy: New Opportunities", *Population Reports*, Series D, No 5, Vol XX, No 1, Mar 1992
2. Finger, W.R., "Using oral contraceptives correctly: progress on package instructions", *Network*, Vol 12, No 2, Sep 1991, pp14-17 and 27
3. WHO, *Injectable Contraceptives*, Geneva, WHO, 1990, p2
4. Mintzes, B., Hardon, A. and Hanhart, J. (eds), *Norplant: Under her Skin*, Amsterdam, Women's Health Action Foundation and WEMOS, 1993
5. Farley, T.M.M., Rosenberg, M.J., et al, "Intrauterine devices and pelvic inflammatory disease: an international perspective", *Lancet*, Vol 339, No 8796, 28 Mar 1992, pp785-8
6. Bounds, W., "Male and female barrier contraceptive methods", chapter 10 in: Filshie, M. and Guillebaud, J. (eds), *Contraception: Science and Practice*, London, Butterworth-Heinemann, 1989, pp172-202
7. Diczfalusy, E., "Contraceptive prevalence, reproductive health and our common future", *Contraception*, Vol 43, No 3, Mar 1991, pp201-27

not believe specific methods are appropriate for an individual woman. Dona Lethbridge, who examined women's perceptions of contraceptive use, reports on the experience of one woman who wanted to change from an IUD to the diaphragm: "When I went to get my IUD out, he (the physician) refused and said I would just get pregnant again. So I had to go to another doctor and she took it out."[6]

Access to safe legal abortion is an important component of birth control strategies. At least 50 million abortions are induced annually throughout the world, many of which are performed illegally.[7] The World Health Organization (WHO) estimates that up to 200,000 maternal deaths a year in developing countries can be attributed to unsafe abortions.[8]

Choice of methods

Choosing the appropriate contraceptive method involves a number of variables, including age, health, frequency of intercourse, and whether the reason for use is to prevent or postpone pregnancy. Those variables will change over time, making it necessary to have a wide variety of contraceptive methods on offer at any time. The box on the next page provides some questions that could help in choosing a contraceptive method.

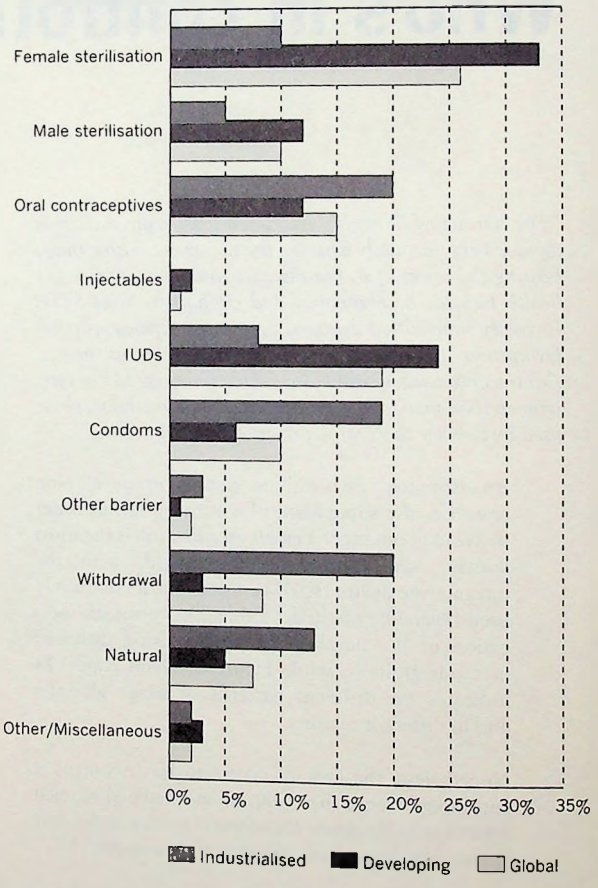
Fundamental to the decision are questions of efficacy, safety, cost and, increasingly, concerns about whether the method provides protection against sexually transmitted diseases (STDs) and human immunodeficiency virus (HIV). Table 8A-2 on the next page indicates how various methods compare in terms of efficacy, safety and protection against STDs.

Safety

Safety is one of the more difficult factors to assess. As British gynaecologist Dr John Guillebaud points out, it is important to avoid damaging health when choosing a contraceptive method. "In trying to find a method of birth control, the main action is to interfere with a *normal* body process and this means taking extra-special care. The method will be used by initially healthy women or men and should not make them unhealthy; on the other hand, it could be used by people who are already unhealthy and must not do them additional harm."[9]

It is worth remembering that all forms of contraception carry some risk. Concern about the safety of the pill (oral contraceptives) and other hormonal contraceptives raises ethical questions about giving a powerful hormone to millions of healthy women. In 1977, reports of increased risk of thrombosis in pill takers – especially smokers – led some women to stop the pill. Two reports in the 1980s that linked oral contraceptives with increased risk of breast and cervical cancer turned many women to the IUD, despite many reports of side effects. The IUD may not be a reversible method for

Figure 8a-1
Percentages of different contraceptive methods used in the 1980s.



Source:
Fathalla, M.F., "Reproductive health in the world: two decades of progress and the challenge ahead", in: Khanna, J., van Look, P.F.A., and Griffin, P.D. (eds), *Reproductive Health: a Key to a Brighter Future*, Geneva, WHO, 1992, p7

some women. Women with IUDs are two to five times more likely to develop pelvic inflammatory disease (PID) than women not using a contraceptive. Risks for users of IUDs who have never given birth may be twice this level. Scarring and blockage of the fallopian tubes from PID is now believed to be the major preventable cause of female infertility.[10]

Longer acting injectable contraceptives can lead to bleeding disorders described in *The Lancet* as "menstrual chaos". Menstrual disturbances are also a problem with implants and, for both methods, long-term safety has yet to be established. There are possibilities of birth defects if a woman becomes pregnant or is already pregnant while using these methods.

The barrier methods of contraception are increasingly popular and have few physical adverse effects. However, they are not always as effective as hormonal methods. The alternatives to hormones or barrier methods are the "natural" methods. The most widely used natural methods – rhythm and withdrawal – are the least effective. The thickness of the cervical mucus and/or early morning temperature can be monitored as indicators of ovulation. This is more effective than rhythm or withdrawal, but requires prior training and consistent monitoring.

Choosing a method

Questions for a woman to consider before choosing a contraceptive method.

1. Are you delaying a first child, spacing your children or not planning to have any (more) children?

2. How would you feel and what would you do if you got pregnant in spite of your method?

3. Will you feel comfortable using this method? Can you talk to your partner about it? Who will use the method, you or your partner? Does your partner feel responsible as well?

4. How well does this method work? Can this method harm you? How much of your body does it affect?

5. How much does it cost?

6. How will this method affect your sexual relationship with your partner?

7. Are there medical reasons why you should not use a particular method?

8. How great is the risk of your getting a sexually transmitted disease, including HIV?

Source: Adapted from: Berer, M., "Contraception", chapter 15 in: Phillips, A., Rakusen, J. (eds) and the Boston Women's Health Collective, *The New Our Bodies, Ourselves* (2nd UK edition), London, Penguin Books, 1989, p277

Table 8A-2
Comparison of some methods of contraception

Method	Pregnancy rate per 100 women[1]	Risk of Adverse effects	Protects against STD/HIV?
Sterilisation			
Male	0–0.2	low	no
Female	0–0.5	medium	no
Oral contraceptives			
combined pill	0.2–7	medium	no
progestogen only	0.3–5	medium	no
Injectables	less than 1[2]	medium-high[5]	no[6]
Implants	0.3–1.4[3]	medium-high[5]	no[6]
IUDs	0.3–9	high	no[7]
Diaphragm	2–20	low	yes/no[8]
Condom	2–20	low	yes
Sponge	9–27	low	yes/no[8]
Spermicide	4–30	low	yes/no[8]
Withdrawal	5–20	–	no
Rhythm	25–30	–	no
Ovulation monitoring	3–25	–	no
Breastfeeding	2[4]	–	no

Notes:
1. Large variations in pregnancy rates for some methods mostly reflect differences in how consistently or well a method is used.
2. The low pregnancy rate with injectables is dependent upon consistent use; this is more likely to occur in clinical trials than in real life situations.
3. The pregnancy rate with implants is higher than this in women weighing more than 70kg.
4. Breastfeeding makes a substantial contribution to birth spacing and fertility control in many areas, and gives a pregnancy rate of less than 2 per 100 during the first six months providing the baby is nearly fully breastfed, and that the mother's menstruation has not returned.
5. Long-term safety of injectables and implants is not certain; also any adverse effects may continue for the duration of the effectiveness of the injection or until after the implant has been removed.
6. Injectables and implants may increase the risk of transmission of HIV if unsterile equipment is used
7. Use of an IUD is a probable risk factor in some STDs.
8. The diaphragm and some other barrier methods reduce the risk of transmission of some STDs, but have no effect on HIV.

Sources: Guillebaud, J., *Contraception: your questions answered*, London, Churchill Livingstone, (revised edn) 1991, pp8 and 201; WHO, *Injectable Contraceptives*, Geneva, WHO, 1990, p20; Anon., "Breastfeeding as a family planning method", *Lancet*, 19 Nov 1988, pp1204-5; Henry, J. (ed.), *The British Medical Association Guide to Medicines & Drugs*, London, Dorling Kindersley, (2nd edn) 1991, p157; Berer, M., "Contraception", chapter 15 in: Phillips, A., Rakusen, J. (eds) and the Boston Women's Health Collective, *The New Our Bodies, Ourselves* (2nd UK edition), London, Penguin Books, 1989, pp271-308

Sterilisation is effective but irreversible and, like all surgery, carries a risk of infection. It is useful for people who are certain they want no more children. [See the sections on *The Pill, IUDs, Injectables,* and *Implants.*]

Sexually transmitted disease

The recent public health focus on AIDS, although well-deserved, has overshadowed a widespread epidemic of STDs. WHO describes the global spread of an estimated 250 million new sexually transmitted infections each year as "one of the major disappointments in public health in the past two decades"[11] (see Table 8A-3).

In rural areas of developing countries, the facilities for the diagnosis and treatment of these STDs are often lacking. One study in two villages in India found that 92% of the 650 women examined had one or more gynaecological or sexual disease, with an average of 3.6 infections per woman. Only 8% of the women had undergone gynaecological examination and treatment in the past.[12] The consequences for women include chronic genital infection, infertility, chronic pain, and death. Infected pregnant women risk higher rates of maternal and infant illness and death. The genital lesions produced by some STDs may increase the risk of contracting or transmitting HIV, the incidence of which is already increasing rapidly among women.[13]

For millions of women, therefore, a prime consideration when choosing a contraceptive may be not only its efficacy in preventing pregnancy, but also its ability to prevent the spread of STDs. An editorial in the *Journal of Clinical Endocrinology and Metabolism* makes the point that:

> "Barrier contraception with condoms... not only prevents pregnancy, but also limits the spread of sexually transmitted diseases."[14]

The condom is currently the only contraceptive which is known to effectively prevent the transmission of HIV. Female condoms can also prevent HIV transmission, but they are relatively expensive and not yet widely available.

Birth control or population control?

No discussion of the risks versus benefits of any form of contraception can be understood without looking at why and how they are used; the social, economic, political and cultural background to the issue. Discussion on the technical merits of one contraceptive over another often ignores these questions entirely.

The development of the pill, and the reliance on the medical profession to dispense it, led to increased intervention in women's fertility. This pattern has continued as a result of research into new types of contraceptives, many of which tend to make women dependent on health workers for their administration and removal. IUDs, injectables and implants all require specially trained health personnel for administration and follow-up, while trained personnel are also required for the removal of IUDs and implants. These "provider-dependent" methods carry the potential for abuse within family planning programmes because a woman who no longer wishes to use the method cannot simply stop; she has to find a health worker to remove the device.[15]

That worry is exacerbated by the recognition that "family planning programmes tend to be more concerned with the welfare of society as a whole than with the well-being of an individual woman."[16]

Through the 1960s and 1970s, the fear of a looming population crisis meant that fertility control became

Table 8A-3
Annual number of new sexually transmitted infections worldwide

Condition	Number of new cases (millions)
Trichomoniasis	120
Chlamydia	50
Human Papillomavirus	30
Gonorrhoea	25
Herpes	20
Syphilis	4
Chancroid	2
HIV	1

Source: Khanna, J., van Look, P.F.A., and Griffin, P.D. (eds), *Reproductive Health: a Key to a Brighter Future*. Geneva, WHO, 1992, p13

An ad for condoms in Pakistan promotes child spacing, QIMP, 1990

a major priority in the funding of both research and aid. By the early 1990s, an estimated $5.3 billion a year was being spent on family planning programmes, with about two-thirds of that amount ($3.5 billion) being spent in developing countries.[17] Between 1970 and 1991, the WHO Special Programme of Research, Development and Research Training in Human Reproduction spent about $310 million, with the annual expenditure during the early 1990s averaging about $22 million.[18]

The US Agency for International Development (USAID) is the "dominant donor" in the population field. In a 10-year period since 1981, USAID contributed some $2.6 billion to population activities, approximately 45% of international population funds. In 1991 alone, USAID spent $330 million on population activities. USAID also provides 75% of the developing world's donor-provided contraceptives. Since 1968, it has supplied 1.6 billion cycles of oral contraceptives, 7.8 billion condoms, and 50 million IUDs.[19]

The development and introduction of the oral contraceptive in the 1960s was heralded in industrialised countries as a revolution in fertility control allowing women to have sex without the fear of pregnancy. In the words of the United Nations Population Fund (UNFPA) in 1985,

> "women in the developed countries already enjoy as a matter of course such basic reproductive freedoms as knowledge of and access to contraception which give them some control over their own fertility."[20]

In developing countries, the starting point was not always the same. Contraceptives have been made available in developing countries not as a means of increasing reproductive options for women, but as part of national population reduction strategies.[21] The reasons for such strategies seemed obvious at the time: there were too many people for the available resources. Limiting population growth would encourage economic and social development. In many cases, the problem had more to do with the distribution and consumption of resources. Nonetheless, the idea that controlling population is *the* way to tackle poverty and development has led to severe distortions in planning and ignored important social justice questions.

In the early 1960s, the US-based Population Council, alarmed at the "problem of unchecked population growth", focused on the IUD as a means of solving the population crisis in developing countries. It convened a conference to encourage the medical profession to look afresh at the IUD as a viable contraceptive method. Participants were assured that two developments made such an approach feasible: new developments in inert plastics that allowed the design of IUDs that could be easily inserted, and the introduction of antibiotics that could cure any infections that occurred. That infections would occur was taken for granted. One leading gynaecologist, Robert Wilson, told the conference,

> "If we look at this from an overall long-range view – these are things that I never said out loud before and I don't know how it is going to sound – perhaps the individual patient is expendable in the general scheme of things, particularly if the infection she acquires is sterilizing and not lethal."[22]

The main goal of many population control schemes was to "motivate" people to see the need for limiting family size. But the rationality of the West (to prevent food shortages or social problems) is not the same as in the developing countries. In many developing countries, people leading subsistence lives rely heavily on their children to augment family income and to take on family responsibilities. John Caldwell, a leading researcher on population studies, has pointed out that subsistence farmers "would be irrational" if they encouraged policies that limited the number of children who could help out with agricultural and household tasks.[23]

Many of the programmes designed to motivate greater acceptance of contraception are aimed at women. Yet, the root of the problem may be with *men's* attitudes. A doctor at a clinic in Mexico notes that "when a wife wants to try to limit the number of mouths to feed in the family, the husband will become angry and even beat her. He thinks it is unacceptable that she is making a decision of her own. She is challenging his authority, his power over her – and thus the very nature of his virility."[24]

In some cases, coercion, strong persuasion, or various inducements were used to encourage contraception. In countries such as Bangladesh, Egypt, India, Indonesia, Pakistan, Taiwan, Thailand, Turkey, Korea and the United Arab Republic, either the acceptors or the promoters of contraception (and sometimes both) have received payments. The payments were either cash or goods and services such as clothing, farm animals, preferential access to housing, or even food.[25]

Where incentives are combined with targets to sterilise, inject, implant, or insert IUDs into a certain number of women a day or month, the idea of a woman having a free choice of methods quickly disappears. Only certain contraceptives are offered to women, often with inadequate warnings on side effects and given by poorly trained health workers under pressure to deliver results. Further, lack of screening and other medical facilities prevent "at risk" women (for example, those with pre-cancerous conditions or already pregnant women) from being identified. As Anrudh K. Jain, a senior associate at the US-based Population Council, explains,

> "With the passage of time, meeting demographic objectives became the overriding concern of organised family planning programmes [that] in certain circumstances... lost track of the underlying principle of meeting individual needs."[26]

For women to be able to make a free choice, they need full information. However, past experience shows that women involved in family planning programmes in developing countries have not always been told the full story about the adverse effects of different contraceptives.[27] It may be in the agencies' best interests *not* to explain side effects or other problems with contraceptive methods. James Shelton, Chief of the Research Division of USAID's Office of Population, said in 1991 that USAID preferred not to use the term "contraindications" when talking about contraceptives. "It is a term which may have very negative connotations and a major inhibitory effect, especially when transmitted downward through the system. A low-level health worker needs a lot of confidence to go against even a 'relative contraindication'."[28]

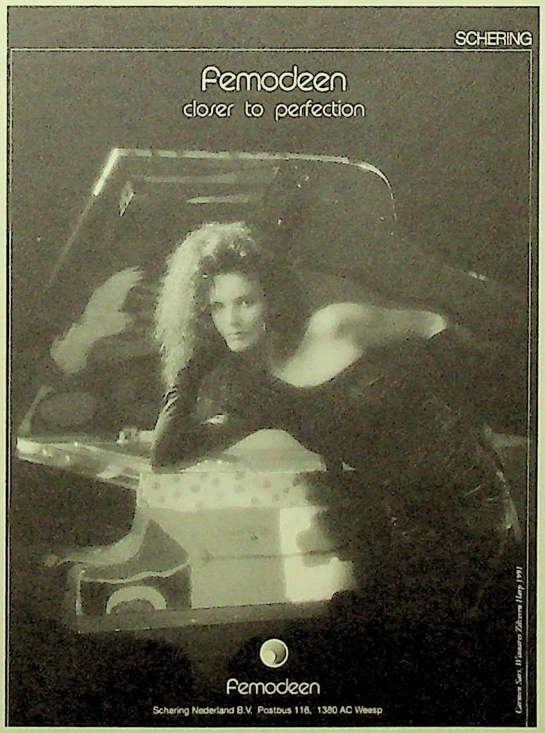
He also identified several "medical barriers" that could hinder the effectiveness and impact of family planning programmes, particularly those that were involved in providing hormonal contraception. Among the "barriers" were: "unnecessary laboratory tests; excessive physical exams (e.g., pelvic and breast);... excessive follow-up schedules;... conservative medical thinking (e.g., taking a woman off the pill for a while if she develops a headache just to play it 'safe');... excessive counselling and history-taking;... categorical exclusion of clients (e.g., by arbitrary age and parity criteria); categorical exclusion of methods (e.g., by not providing IUDs because the STD rate is too high in the population)...." Many of these tests and exclusion criteria are seen as a routine part of safe provision of contraceptives in industrialised countries.

At the root of the controversy is the difference between the concept of population control – something imposed from outside – and the concept of birth control, birth spacing and family size – decisions that ought to be made by the individuals most concerned: women and their partners. Women, not governing institutions, "are the rightful arbiters of women's birth-control requirements."[29]

Jayne Maranga, a Kenyan woman who works in the Nairobi office of the UK-based Voluntary Services Overseas, makes the point that for women in Kenya,

> "especially those who have never been to school, there is still confusion as to the difference between family planning and birth control. Most of them have interpreted what the government is saying to mean that they should stop having children. This is seen as a foreign concept and it is important that the organisations concerned make it clear that it is only through planned parenthood that our children can be adequately provided for."[30]

In recent years, there are some indications that more informed attitudes and behaviours are occurring in family planning programmes. Increasingly, the complex interaction of social, economic and cultural factors that maintain high levels of population growth in some parts of the world are being addressed in a more holistic manner rather than relying on the technological response of controlling population first. According to the United Nations Population Fund, "raising the status of women in developing countries by giving them access to adequate education, health care, and work at a fair wage is an essential part of slowing population growth and thus reducing poverty."[31]



Schering advertises an oral contraceptive to doctors in the Netherlands, The Practitioner, March 1992

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Searching for alternatives

With many women dissatisfied about current contraceptive methods, and with the importance given to contraception generally, it is not surprising that a great deal of research is underway to find better methods. However, the search for alternatives is limited by the same sorts of forces that drove research towards female hormonal contraceptives in the first place. Research continues to focus mainly on hormonal or provider-dependent methods to be used by women, while alternatives are largely rejected. This has led one gynaecologist to comment that contraceptive researchers

> "would do better to concentrate their resources on making the *safe methods more effective*.... Concentrating on improving these methods is surely better than the conventional wisdom of the scientific establishment, which starts with current or innovative systemic methods which are highly effective and convenient, and then strives diligently towards making them risk-free. Success down that road will be nearly as impossible to prove as it ever will be to achieve!"[32]

Among the areas being looked at the moment are: male contraceptives, a contraceptive vaccine, and an abortion pill.

Male contraceptives

Research on male contraceptives has been slow. Weekly injections of the male hormone testosterone have been found to maintain "safe, stable, effective and reversible contraception for at least 12 months", although the frequency of injections was a major cause for discontinuation. Also, as with the injectable contraceptive for women, the long-term risks are not known, although both prostatic cancer and cardiovascular disease are potential risks.[33] Animal studies on a combination of testosterone with a chemical to inhibit the secretion of gonadotrophin releasing hormone have successfully prevented sperm production in primates, and such a product is predicted to have a similar effect in humans,[34] although whether it will prove to be safe and acceptable is still in doubt.[35]

Another chemical, gossypol, a substance found in raw cotton seed oil, can reduce sperm production, but has been shown to inhibit sexual desire in animal studies.[36] Human studies have also raised the possibility that as many as 10% of users may become permanently sterile.[37]

However, a male contraceptive – other than improving condoms and encouraging increased use – is unlikely to emerge in the near future. Even if a promising substance is identified, today's "stringent toxicological studies and licensing procedures compared with 25 years ago when the female pill was first widely available" will slow down the development process.[38]

A contraceptive vaccine?

Optimists suggest that a birth control vaccine for women could be in use within 15 years, with the most likely candidate being a vaccine that targets human chorionic gonadotrophin (hCG) – a hormone that is produced during pregnancy. Blocking the action of the hormone interferes with the ability of the embryo to implant in the womb.[39]

Research is also underway to find a vaccine that prevents fertilisation by interfering with the proteins contained in either the sperm or the egg. One such vaccine, developed by scientists at the University of Virginia in the USA, is expected to go into clinical trials by 1994. It acts by stimulating the production in the woman of antibodies to a particular protein that is believed to be present in all human sperm. The binding of the antibodies to the protein will prevent the sperm from fertilising the egg.[40]

Another team is looking at a vaccine that will develop antibodies to a protein on the surface of the egg. The binding of the antibodies to the protein will effectively keep out the sperm.[41]

The as yet unproven hypothesis is that these vaccines are likely to be relatively side effect free. WHO also says that they would be "easy to administer and would be comparatively inexpensive".[42] However, there are many safety and efficacy questions that need to be resolved. The effect if a woman is already pregnant or becomes pregnant while using these vaccines is not known. Also, because of the variation in immune responses in individual women, the actual period of efficacy cannot be accurately predicted.[43] Although a more traditional vaccine sets up an immune response to an external toxin entering the human system, these anti-fertility vaccines are trying to provoke an auto-immune response – that is, they are targeted on interfering with the normal functioning of the human body and its immune system. With the increased prevalence of diseases that attack the human immune system, is it wise to develop a vaccine that may make it easier for those attacks to take root?

As Carl Djerassi, the chemist who produced the first orally active progestogen, norethisterone, in 1951, has pointed out recently, "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."[44]

An abortion pill?

Some of the most controversial contraceptive research in recent years has focused around the development and introduction of an antiprogestogen called mifepristone that is sometimes better

known by its drug testing identification number, RU486. The drug, manufactured by Roussel Uclaf, prevents the functioning of the hormone progesterone, which is essential for a successful pregnancy. It has been licensed in France, China, Sweden and the UK for the medical termination of pregnancy (abortion), provided that a prostaglandin analogue (such as gemeprost) is administered two days later.[45] It has been shown to be effective in about 95% of cases if it is taken by the 7th week of pregnancy.

Popularly known as the "abortion pill", mifepristone has been both hailed and condemned, depending on attitudes towards abortion. Carl Djerassi described mifepristone as "the most significant research achievement of the 1980s in new practical fertility control".[46] Sir Malcolm Macnaughton, Professor of Obstetrics and Gynaecology at the University of Glasgow, said it was "an advance in reproductive medicine of the same magnitude as the development of the hormonal contraceptive pill".[47] Threats of a boycott by the anti-abortion lobby led Roussel Uclaf to announce at one point that it would suspend distribution of the drug in France, only to reintroduce it two days later on the instruction of the French Minister of Health who described it as the "moral property of women".[48] In 1991, two anti-abortion groups called on UK doctors to boycott products manufactured by Roussel and its parent company, Hoechst.[49] In the USA, the pressure from the anti-abortion lobby has led to a reluctance on the part of Roussel to seek registration of the drug, despite calls for clinical research on mifepristone by the American Medical Association and the American Association for the Advancement of Science.[50] It also led to an "import alert" from the US Food and Drug Administration banning personal importation of mifepristone on the grounds that medical supervision was required for proper use.[51]

In developing countries, Roussel originally had a distribution agreement with WHO, although Professor Etienne-Emile Baulieu, who developed the drug, has accused Roussel and WHO of blocking the product's marketing worldwide because of political pressure.[52] An indication of the kind of political pressure being levelled on WHO is evident in the request from the US State Department to WHO to ensure that no US funds were being used to promote the use of the drug. It also asked whether WHO was recommending the use of the drug in countries where medical supervision is unlikely.[53] Roussel announced in May 1993 that it would license the drug and make it over to the Population Council. The Population Council would then be responsible for finding a manufacturer and conducting the necessary clinical trials to enable wider use of the drug.[53a]

Professor Baulieu claims that mifepristone could be most useful in developing countries, even though there is the possibility that it could be used in less stringent conditions than those in force in France and the UK.[54] Other commentators are more cautious, pointing out that "in many developing countries women with unwanted pregnancies face not only poor access to medical care but also the illegality of abortion unless medically indicated. In such circumstances, it is likely that these drugs will only be available on the black market, at a price, and proper information on the drugs will not be available."[55] Edouard Sakiz, chairman of Roussel, said in 1990 that "the quickest way to sabotage the product and its usage procedures would be to market it as it is in Third World countries". He said that health authorities in China and India had said that "it would be impossible to control a product of that kind in their countries."[55a]

The controversy around mifepristone is likely to continue throughout the 1990s. It is likely to be some time (if ever) before widespread use of a product like mifepristone will become a reality. Many questions must still be resolved about the use of this type of abortifacient. A safety issue, that also has bearing on the need for adequate health services, is what happens in the 5% or more (with improper use) of cases where a pregnancy is not successfully terminated? Prostaglandins have been reported to be teratogenic in humans, so the availability of an alternative means of termination is essential.[56] This means that the abortion pill is not a do-it-yourself substitute for vacuum aspiration abortions.[57] Roussel's chairman has stated clearly that using mifepristone is much more complex than vacuum aspiration. "It's an appalling psychological ordeal" for the woman.[57a] In any case, vacuum aspiration is an effective and relatively safe method of abortion. The problem is not the method, but lack of access to it in developing countries. The abortion pill is not an appropriate answer to a series of social, cultural, political and economic constraints that make it difficult for women to have access to safe, legal abortions.

Natural family planning and breastfeeding

The difficulties that now exist in the field of contraceptive development have provided an opportunity to take a fresh look at natural family planning (NFP).[58] NFP methods have been described as "probably the methods of choice" for developing countries because they are simple, inexpensive (requiring only some educational input), free of side effects, and acceptable to most cultures and religions.[59] An international study conducted by WHO found that couples who used the methods correctly (daily monitoring of temperature and cervical mucus for eight cycles) were able to achieve a contraception rate of 97%. The study also found that 94% of women could identify the fertile phase after a training period that covered three cycles.[60]

Breastfeeding, long hailed as the single most important method of birth spacing, is now often incorporated into NFP programmes. Studies have shown that when a baby is nearly fully breastfed for the first six months and when menstruation has not returned, ovulation fails to occur. This lactational amenorrhoea method (LAM) provides at least 98% protection against pregnancy.[61]

Breastfeeding also significantly lowers the risk of both ovarian and breast cancer. For example, the risk of breast cancer for women who breastfeed is half that of women who do not breastfeed.[62] Including breastfeeding as part of a natural family planning programme may be a way of ensuring contraceptive protection while promoting infant health, as exclusive breastfeeding provides the best possible nutrition during the first four to six months of life.

Recommendations for action

Family planning programmes will be more effective if reproductive services incorporate the Essential Drug and Primary Health Care concepts: fertility regulating services should be comprehensive, including maternal and child health care and other health services, accessible to everyone, irrespective of age, sex or marital status. Paying attention to women's overall reproductive health may lead to safer choices of contraception.

For this to happen, women and men should have a free choice of methods and balanced information. This involves meeting basic criteria such as those set out in the WEMOS and HAI *Guidelines for the Distribution and Use of Fertility Regulating Methods*:[63]

1. a wide range of contraceptive methods as well as safe abortion and sterilisation to choose from;
2. full, unbiased information about the contraceptive options available; their risks, their benefits, clear instructions about how they should be used, and the possible impact they will have on personal relationships and daily life;
3. an opportunity to decide on which method to use free from sanctions or incentives;
4. access to a good health care system because many methods are provider-dependent, and require settings where the user has access to follow-up care, and where removal on demand is assured.

Research efforts should also be expanded to improve the availability and convenience of existing user-controlled methods of contraception including barrier and natural methods.

Above all, improving the political, economic and social status of women and involving them more fully in the design and implementation of family planning programmes is liable to have the most long-lasting impact.

References:

1. Khanna, J., van Look, P.F.A., and Griffin, P.D. (eds), *Reproductive Health: a Key to a Brighter Future*, Geneva, WHO, 1992, p4
2. Ibid, p6
3. DaVanzo, J., Parnell, A.M., and Foege, W.H., "Health consequences of contraceptive use and reproductive patterns: Summary of a report from the US National Research Council", *Journal of the American Medical Association*, Vol 265, No 20, 22/29 May 1991, pp2692-6
4. Jacobson, J.L., *Women's Reproductive Health: the silent emergency*, (Worldwatch Paper 102), Washington, Worldwatch Institute, 1991, p52
5. Lethbridge, D.J., "Choosing and using contraception: toward a theory of women's contraceptive self-care", *Nursing Research*, Vol 40, No 5, Sep-Oct 1991, pp276-80
6. Ibid
7. Filshie, M., "Abortion", chapter 14 in: Filshie, M. and Guillebaud, J. (eds), *Contraception: Science and Practice*, London, Butterworth-Heinemann, 1989, pp250-74
8. Potts, M. and Rosenfield, A., "The fifth freedom revisited: I, background and existing programmes", *Lancet*, Vol 336, 17 Nov 1990, pp1227-31
9. Guillebaud, J., *The Pill*, Oxford, Oxford University Press, (4th edn) 1991, p227
10. Jacobson, op cit, pp32-3
11. Khanna, et al, op cit, p13
12. Bang, R.A., Bang, A.T., et al, "High prevalence of gynaecological diseases in rural Indian women", *Lancet*, No 8629, 14 Jan 1989, pp85-8
13. Jacobson, op cit, p28
14. Winters, S.J. and Marshall, G.R., "Editorial: Hormonally-based male contraceptives: will they ever be a reality?", *Journal of Clinical Endocrinology and Metabolism*, Vol 73, No 3, 1991, pp464A-B
15. Hardon, A., "Contraceptive research: women's perspectives", in: Mintzes, B (ed.), *A Question of Control: Women's Perspectives on the Development and Use of Contraceptive Technologies*, Amsterdam, WEMOS Women and Pharmaceuticals Project/HAI, 1992, p7
16. Lethbridge, op cit, pp276-80
17. Brown, P., "Cash for contraception will keep family sizes falling", *New Scientist*, 18 May 1991, p15
18. Khanna, et al, op cit, p139
19. Spieler, J., "US Agency for International Development: Support for NFP", in: Queenan, J.T., Jennings, V.H., et al, *Natural Family Planning: Current Knowledge and New Strategies for the 1990s*, (Proceedings of a conference held at Georgetown University, 10-14 Dec 1990), Washington, DC, Georgetown University, Apr 1992, p6
20. UNFPA, *1984 Report*, New York, UNFPA, 1985, p8
21. LaCheen, C., "Population control and the pharmaceutical industry", in: McDonnell, K. (ed.), *Adverse Effects: Women and the Pharmaceutical Industry*, Penang, IOCU, 1986, p90
22. Pappert, A., "The rise and fall of the IUD", in: McDonnell, op cit, p168
23. Lappé, F.M. and Schurman, R., *Taking Population Seriously*, London, Earthscan Publications, 1989, p22
24. Ibid, pp26-7
25. Ibid, pp40-2; LaCheen, op cit, pp120-24
26. Jacobson, op cit, p39
27. Lappé and Schurman, op cit, p45
28. Letter from James D. Shelton, Chief, Research Division, and Cynthia Calla, Medical Officer, Family Planning Services Division, of the Office of Population, USAID, Washington, DC, to Carlos Huezo, Medical Director, International Planned Parenthood Federation, London, 21 Aug 1991
29. Jacobson, op cit, p52
30. Maranga, J., "A question of education", *Orbit*, Autumn 1988, p14
31. United Nations Population Fund, *The State of the World Population 1992*, New York, 1992, cited in: Anon., "Women's status and world population", *Lancet*, Vol 339, 2 May 1992, p1107
32. Guillebaud, J., *Contraception: your questions answered*, London, Churchill Livingstone, (revised edn) 1991, pp293-4
33. WHO Task Force on Methods for the Regulation of Male Fertility, "Contraceptive efficacy of testosterone-induced azoospermia in normal men", *Lancet*, Vol 336, 20 Oct 1990, pp955-9
34. Bremner, W.J., Bagatell, C.J. and Steiner, R.A., "Gonadotropin-releasing hormone antagonist plus testosterone: a potential male contraceptive", *Journal of Clinical Endocrinology and Metabolism*, Vol 73, No 3, 1991, pp465-9
35. Winters and Marshall, op cit, pp464A-B
36. Taylor, G.T., Griffin, M.G. and Bardgett, M., "Search for a male contraceptive: the effect of gossypol on sexual motivation and epididymal sperm", *Journal of Medicine*, Vol 22, No 1, 1991, pp29-44
37. Jeffcoate, S.L., "Progress towards a systemic male contraceptive", chapter 17 in: Filshie and Guillebaud, op cit, pp305-9
38. Ibid
39. Grubb, G.S., "Experimental methods of contraception", *Current Opinion in Obstetrics and Gynecology*, Vol 3, 1991, pp491-5
40. Anon., "Ortho's contraceptive vaccine", *Scrip*, No 1687, 29 Jan 1992, p26
41. Pain, S., "Hopes grow for 'perfect' contraceptive", *New Scientist*, 2 Mar 1991
42. Khanna, et al, op cit, p91
43. Hardon, A., "An analysis of research on new contraceptive vaccines", *Women and Pharmaceuticals Bulletin*, Nov 1990, pp22-4
44. Djerassi, C., "The bitter pill", *Science*, Vol 245, July 1989, pp356-61
45. Khanna, et al, op cit, pp98-9; Anon., "Mifepristone approved in Sweden", *Scrip*, No 1752, 11 Sep 1992, p27
46. Djerassi, op cit, pp356-61
47. Anon., "UK approval for mifepristone", *Lancet*, Vol 338, 13 Jul 1991, pp111-2
48. Williams, C. (ed.), *The "Abortion Pill": widening the choice for women*, London, Birth Control Trust, 1990, p6
49. Anon., "UK pro-lifers boycott Roussel/Hoechst", *Scrip*, No 1656, 1 Nov 1991, p7
50. Potts, M., "USA: Access to mifepristone", *Lancet*, Vol 339, 9 May 1992, pp1161-2
51. Charo, A., "USA: Personal importation of mifepristone", *Lancet*, Vol 340, 25 Jul 1992, p229
52. Anon., "Prof Baulieu on mifepristone", *Scrip*, No 1542, 22 Aug 1990, p19
53. Anon., "New York Mayor's mifepristone campaign", *Scrip*, No 1608, 17 Apr 1991, p18
53. Anon., "Mifepristone", *Lancet*, Vol 341, 1 May 1993, p1146
54. Anon., *Scrip*, No 1542, op cit, p19
55. Fonseca, W., Misago, C. and Kanji, N., "Misoprostol plus mifepristone", *Lancet*, Vol 338, 21/28 Dec 1991, p1594
55a. Nau, J.-Y., "Drug firm defends marketing strategy on abortion pill", *Guardian Weekly*, 19 Aug 1990 (from an article in *Le Monde*, 1 Aug 1990)
56. Silvestre, L., Dubois, C., et al, "Voluntary interruption of pregnancy with mifepristone (RU 486) and a prostaglandin analogue: a large-scale French experience", *New England Journal of Medicine*, Vol 322, No 10, 8 Mar 1990, pp645-8
57. LeGrand, A., "The abortion pill: A solution for unsafe abortions in developing countries?", *Social Science and Medicine*, Vol 35, No 6, 1992, pp767-76
57a. Nau, J.-Y., op cit
58. Kambic, R.T., "Natural family planning use-effectiveness and continuation", *American Journal of Obstetrics and Gynecology*, Suppl. to Vol 165, No 6, Part 2, Dec 1991, pp2046-2048
59. Ryder, R.E.J., "Abortion", *Lancet*, Vol 339, 20 Jun 1992, p1544
60. Queenan, J.T. and Moghissi, K.S., "Natural family planning: looking ahead", *American Journal of Obstetrics and Gynecology*, Suppl. to Vol 165, No 6, Part 2, Dec 1991, pp1979-80
61. Gross, B.A., "Is the lactational amenorrhea method a part of natural family planning? Biology and policy, *American Journal of Obstetrics and Gynecology*, Vol 165, No 6, Part 2, Dec 1991, pp2014-19
62. Labbok, M. and Koniz-Booher (eds), *Breastfeeding: protecting a natural resource*, Washington, Georgetown University, 1990, p8
63. WEMOS/HAI, *Guidelines for the Distribution and Use of Fertility Regulation Methods*, Amsterdam, WEMOS/HAI, 1991

Chetley, A. *Problem Drugs*, Amsterdam,
Health Action International, 1993

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8B. The pill

Lowering the risks

Oral contraceptives are among the most widely used prescription drugs,[1] the most widely researched,[2] and, "with an incredible profit margin", are among "the most profitable of all pharmaceuticals".[3] First introduced in the 1960s, they are now used by more than 63 million women worldwide every day,[4] 46 million of them in developing countries.[5] The world market for oral contraceptives was estimated at $1.8 billion in 1989.[6] In the UK in 1987, approximately 45% of women aged 20-29 were using "the pill". Although only about 40% of women born in the 1930s had ever used the pill, about 80% of those born in the 1950s had used it.[7] In the US in 1991, 28% of women between the age of 15 and 44 were using oral contraceptives, the highest level since 1975.[8] By 1995, the US market for oral contraceptives is expected to be worth some $1.4 billion dollars.[9] However in Mexico, where the pill was the most-widely used contraceptive in the 1970s, it is now less popular than injectable contraceptives, the intrauterine device (IUD) and sterilisation. The reason: Mexican women believe that the pill is more likely than other contraceptives to cause harmful side effects.[10]

Efficacy

Because the pill is taken by generally healthy women, it is even more important that it should be extremely safe as well as effective. Its effectiveness, when used correctly, is not in doubt: with the combined oral contraceptive (COC) containing two synthetic hormones, an oestrogen and a progestogen, pregnancy occurs in less than one in 100 women per year.[11] The rates are similar for the newer "phased" COCs that contain varying amounts of hormones in an attempt to mimic the body's own pattern of production of hormones. Pregnancy rates for women using a progestogen-only pill (POP) are higher, ranging from one to three per 100 women years.[12] The COC functions by preventing ovulation – creating a simulated pregnancy – as well as making the cervical mucus less penetrable by sperm and making the lining of the uterus less receptive to implantation of a fertilised egg. With the POP, the main effects are on the mucus and uterus lining, although some disruption of the ovulation cycle also occurs.

The effectiveness, of course, depends on the pills being taken regularly. Recent research has shown that from six to 20% of pill users may become pregnant because of incorrect use.[13] Most COCs are taken for 21 days, followed by a seven day pill-free time (or seven days of a placebo pill). If a pill is omitted for more than 12 hours, alternative contraception, such as a condom or other barrier method, should be used along with the pill during the next seven days. Pills missed near the beginning or end of the cycle are particularly likely to increase the risk of ovulation and hence of pregnancy.[13a]

Effectiveness can also be altered by interactions with other drugs. In particular, drugs which may diminish absorption by causing gastrointestinal disturbances or inducing enzymes, such as antibiotics, antifungal drugs, anticonvulsants or barbiturates, have been identified as reducing the efficacy of oral contraceptives.[14] There is also some evidence that smoking – in addition to being linked with an increased risk of cardiovascular adverse effects among pill users – could reduce the efficacy of the pill.[15]

Safety

The safety profile is more controversial. In the late 1970s, it became clear that women using the pill had an increased risk of thrombosis and other vascular disorders – especially if they were smokers. A study by the Royal College of General Practitioners in 1983 found a four-fold increased risk of death from arterial diseases in COC users. The report also showed that the pill user who smoked was not only more likely to suffer an arterial disease event (chiefly a heart attack

or stroke) but was also much more likely to die as a consequence. Deep venous thrombosis, pulmonary embolism, myocardial infarction, thrombotic strokes, haemorrhagic strokes and other arterial diseases have been shown to be commoner in COC users.[16]

The pill and breast cancer

In 1983, another concern surfaced about the pill. Two studies linked the pill with cancer. The first, by Professor Malcolm Pike and his colleagues in Los Angeles, suggested that women under 25 who took a COC with a high progestogen content for five years ran a four-fold risk of getting breast cancer. The second study, by Professor Martin Vessey and his colleagues at Oxford University, suggested that women using COCs ran a 75% greater risk of developing cervical cancer than those using an IUD. Both reports, published in the same issue of *The Lancet*, stirred up controversy.[17]

Since then, both studies have come in for considerable reassessment and additional research has looked for other associations which could explain the results. A 1989 study in the UK found that women under 36 years of age who used an oral contraceptive for more than eight years ran a 74% increased risk of developing breast cancer, while the increased risk was 43% for those who had been using the pill for between four and eight years.[18] The Nurses' Health Study in the USA, which has been monitoring nearly 120,000 women for more than 10 years, concluded that "past use of oral contraceptives is not associated with a substantial increase in breast cancer".[19] A detailed analysis of data from the Cancer and Steroid Hormone Study (CASH study) in the USA concluded that "oral contraceptive use appeared to increase slightly the risk of breast cancer for women aged 20-34 years of age, did not appear to affect the risk of breast cancer for women aged 35-44, and appeared to confer a slightly decreased risk of breast cancer for women aged 45-54 years".[20] It noted that caution was needed in interpreting the findings because the range of increase or decrease of risk was quite small.

A comprehensive epidemiological review published in 1992 concluded that "there is no consistent evidence of an association between progestins and breast cancer".[21] A review of case-control studies, published in 1991, used data collected principally in the 1980s by well recognised research groups observing strict protocols. This review concluded that there was a "strong consensus that oral contraceptives have not increased the risk of breast cancer in women over age 45, even when they have been used for long periods". It also found that among younger women, the evidence for a causal relationship between oral contraceptives and breast cancer was insufficient.[22] A second 1991 review concluded that oral contraceptives "have caused little or no overall increase in the risk of breast cancer in women in developed countries". It added that "limited information from developing countries... suggests that use of oral contraceptives may moderately enhance risk in women in low risk populations". In other words, women who would not normally be expected to develop breast cancer may be more at risk.[23]

Despite more than three decades of use, the evidence about the links between the pill and breast cancer is still inconclusive. There is little information available regarding the risk to women who start using the pill when they are very young – often the very women for whom the pill is the most popular form of contraception.[24] As one researcher points out, "it is possibly too soon to know what the long-term effects of using oral contraceptives while young on breast cancer actually are".[25] Partly this is because of the constant changes in dosage levels of oral contraceptives over the last 30 years which makes accurate comparison of effects over time difficult,[26] and partly it has to do with the difficulty in establishing possible causes of breast cancer generally.

Risk of cervical cancer

On the question of oral contraceptives and cervical cancer, Vessey himself subsequently said that "although the balance of evidence suggests quite strongly that prolonged oral contraceptive use slightly increases the risk of cervical cancer", it was "impossible to be sure that the effect is not due to incompletely controlled confounding by sexual factors."[27] Nevertheless, he considered it important for women using an oral contraceptive to have an annual cervical examination.

A WHO study carried out in eight developing and three industrialised countries found a 20% increased risk of cervical cancer among oral contraceptive users in developing countries. However, the report also noted that "the observed increase in risk in users may be due to behavioural characteristics of users or their male partners conducive to the spread of sexually transmitted diseases".[28] In contrast, use of barrier methods of contraception, such as the diaphragm, led to a reduction in the risk of cervical cancer by as much as 75%.[29]

AIDS and the pill

One barrier method of contraception – the condom – is now a valuable tool in public health efforts to combat the spread of sexually transmitted diseases (STDs) in general and acquired immunodeficiency syndrome (AIDS) in particular. In the light of evidence that shows increases in the heterosexual spread of AIDS, a new factor needs to be considered when decisions are made about choices of contraceptives. A major disadvantage of the pill is that it does not provide any protection from STDs, nor from the human immunodeficiency virus (HIV) causing AIDS. In Japan, for example, where 80% of married couples use the condom for contraception, the government has consistently

delayed issuing a licence for low-dose contraceptive pills. The reason is cited as being concern that availability of the pill might contribute to the spread of HIV infection in Japan.[30]

Several studies have suggested that hormones in the pill can modify immune mechanisms. "The effects are of a similar nature to, but less marked than, those associated with pregnancy.... The prospective studies have shown an increase in inflammations and some disorders which are believed to have an immune basis."[31] Taking a drug which might challenge the human immune system itself, albeit in a minor manner, should not be a light decision. This is particularly important when considering the usual group of women who use the pill.

The pill is often prescribed for young, sexually active women who may have multiple sexual partners (or whose partners may be sexually involved with others). They are among the groups with the greatest risk of STDs and AIDS, and a major consideration should be a choice of contraceptive that protects against more than simply pregnancy. In today's world, the pill may not be the prime choice.

Wyeth advertises the "unsurpassed safety profile" of the oral contraceptive Nordette in Pakistan in 1990 without any information on risks of serious adverse effects or comparisons to risks of other contraceptives.

Other adverse effects

The risk of liver cancer is increased among pill users.[32] Because liver cancer is rare, the absolute risk is quite low, but it nonetheless exists. Pill users also have an increased risk of gall bladder disease and of gallstones.[33]

Because the COC causes a hormonal change similar to a state of pregnancy, many of the frequent side effects resemble those of pregnancy. The most commonly reported adverse effects include: nausea, vomiting, headache, tenderness of the breasts, changes in body weight, thrombosis, loss of libido, depression, brown pigmentation on the face (chloasma), raised blood pressure, impaired liver function, reduced menstrual loss, "spotting" early in the cycle, loss of periods, and (rarely) sensitivity of the skin to sunlight.[34]

A common complaint from pill users is depression. It has been reported in both the COC and POP pills.[34a] "Norethisterone particularly seems to be related to depression of mood."[35] However, norethisterone has one of the lowest ratings for progestogen potency, and is therefore a frequently used progestogen in COCs.

Possible advantages

The pill has been shown to have some advantages in addition to its effectiveness as a contraceptive. Among these are predictable menstrual periods with less blood loss, and less risk of fibroids and of benign breast disease.[36] Oral contraceptive use decreases the risk of pelvic inflammatory disease by about 50%, although some evidence suggests that the use of the pill leads to a two to threefold increase in chlamydia infections of the cervix.[37] Ovarian cancer, which is rare, and cancer of the endometrium (the lining of the uterus) are less common among oral contraceptive users.[38] Women who use an oral contraceptive for as little as six months have 40% less risk of developing ovarian cancer for up to 15 years after use. Women who use an oral contraceptive for at least a year have about half the risk of endometrial cancer. In both cases, the greatest protective effect is evident among women with few or no children – those who are usually at the highest risk of these types of cancer.[39]

Contraindications

The pill should not be used by women who are pregnant, have a history of thrombosis or jaundice, have previously been exposed to diethylstilbestrol (DES), or who have liver disease, sickle cell anaemia, high blood fat levels, cancer of the breast or womb, severe migraine, undiagnosed bleeding from the vagina, history of severe itching (pruritus) in pregnancy or deteriorating otosclerosis (a condition which causes hearing loss). The pill should not be the first choice contraceptive for women who suffer from obesity, diabetes, raised blood pressure, heart or kidney disease, mild migraine, epilepsy, depression, asthma, multiple sclerosis, who wear contact lenses, have varicose veins, smoke, are over 35 years of age, or are breastfeeding.[40]

Selecting the right pill

Identifying who could use the pill is the first step towards more rational use. The second is deciding which pill to use. There is now almost universal acceptance that low-dose pills are best.

> "Safer pills are *smaller* pills (i.e. lower dose). The dose of ethinyloestradiol (EE) should be no more than 30-35 mcg combined also with a low dose of the selected progestogen – both hormones being capable of unwanted metabolic effects and their epidemiological consequences. The dose of both the oestrogen and the selected progestogen should be the lowest acceptable in the individual woman. Latest data suggest that this policy really does reduce the risk of major side effects. Clinical experience shows that minor side effects also (apart from those linked with the bleeding pattern) are less frequent and less severe."[41]

The American Medical Association (AMA) says, "as a general rule, preparations containing the smallest quantity of steroid consistent with efficacy and tolerable side effects are preferred. This means selection of a product containing less than 50 mcg of estrogen for a first-time user."[42] Because higher-dose oestrogen formulations are associated with a greater incidence of adverse effects without greater efficacy, the US Food and Drug Administration (FDA) has recommended that they no longer be marketed in the United States.[43] The FDA has also warned oral contraceptive manufacturers not to use unfounded claims in their promotional materials in an attempt to define non-existent differences among the low-dose pills. According to the FDA, "there have been no data submitted to the agency which demonstrate that the differences being cited in the promotion of low-dose oral contraceptives indeed exist, and if so, are clinically relevant."[44]

The UK Committee on Safety of Medicines has recommended that "women receiving oral contraceptives should be prescribed a product with the lowest suitable content of both oestrogen and progestogen."[45]

Progestogen-only pills "are suitable for older patients who may be at risk from oestrogen, heavy smokers, and those in whom oestrogens cause severe side-effects."[46] Because the POP does not interfere with the quantity of breast milk and only very tiny amounts of the hormone have been shown to get into the milk, POPs are widely used by women who are breastfeeding.[47] However, because hormones might affect the endocrine balance in the infant [47a] and long-term effects are not known, it is preferable to use a non-hormonal form of contraception while breastfeeding.

No matter which pill is selected, "patients require periodic evaluation for side effects."[48] According to the AMA, "Patients taking OCs should be monitored regularly. Biannual [every six months] blood pressure measurement and annual physical examination, including urinalysis, liver palpation, and breast and pelvic examinations... should be performed.... Patients should be encouraged to examine their breasts monthly."[49]

Regular examinations are unlikely in many developing countries. In some countries, programmes to distribute contraceptive pills explicitly target those who do not have access to health care. This means that women with high-risk conditions may be more likely to use the pill and that follow-up medical attention may be more difficult to find in the event of unpleasant or dangerous adverse effects.[50]

Sensible use in developing countries is also complicated by the abundance of different types of pills on the market. Dr John Guillebaud, a gynaecologist and expert in family planning, answers the question "which COC brands are unacceptable for normal prescribing?" by stating:

> "First, the 50 mcg oestrogen brands, since the aim of effective contraception is achievable with less oestrogen in most cases.... Secondly, the brands giving 250 mcg of levonorgestrel (Eugynon 30, Ovran 30) and 2000 mcg of ethynodiol diacetate (Conova 30) are unbalanced.... Their use should be restricted mainly to gynaecological indications.... Microgynon/Ovranette and Neocon/Norimin alter lipids adversely enough to be no longer first choice pills for women starting the method."[51]

Another brand which is of dubious value is Loestrin 20, described by the *British National Formulary* as "less suitable for prescribing" because the amount of oestrogen present may be too small to provide adequate contraception.[52]

During the 1980s, there has been "a dramatic shift" to low-dose oral contraceptives, particularly in industrialised countries. According to IMS – an international market research firm – by 1987 low oestrogen pills accounted for 85% of all pharmacy purchases of COCs in 18 industrialised countries and about 60% in 19 developing areas.[53] Even so, as the table on page 161 indicates, more than 40% of the 87 oral contraceptives on the market in four regions of the Third World during 1990 and 1991 could be considered as less suitable for prescribing – usually because the level of oestrogen was at the highest acceptable level coupled with a high level of progestogen potency, or because they were unbalanced, with an excessive progestogen content.

[See also the sections on: *Contraceptives, IUDs, Injectables*, and *Implants*]

Table 8B-1
Oral contraceptives on the market in selected areas (1990-1)

Brand name & company	OES mcgs.	PRO mgs.	PRO POT	Type of progestogen	Availability
First choice					
Brevinor (Syntex)	35	0.50	L	norethisterone	A, C, M
Gynera (Schering AG)	30	0.08	L	gestodene	M
Loestrin 30 (Parke-Davis)	30	1.50	L	norethist. acet	A
Marvelon 28 (Organon)	30	0.15	L	desogestrel	P
Minulet (Wyeth)	30	0.08	L	gestodene	A
Ortho Novum 1/35 (Ortho)	35	1.00	L	norethisterone	C
Ortho Novum 7-7-7 (Ortho)	35	0.75	L	norethisterone	C
Ovysmen (Ortho-Cilag)	35	0.50	L	norethisterone	A, M
Synphase (Syntex)	35	0.71	L	norethisterone	C, M
Trinovum (Cilag)	35	0.75	L	norethisterone	A
Second choice					
Anteovin (Medimpex)	50	0.13	M	levonorgestrel	A, C, M
Logynon/ED/Triquilar(Schering)	32	0.09	M	levonorgestrel	A, C, M
Lyndiol (Organon)	50	2.50	M	lynestrenol	A
Minovlar 21 (Schering)	50	1.00	L	norethist. acet	P
Non-Ovlon (Germed)	50	1.00	L	norethist. acet	M
Norimin (Syntex)	35	1.00	L	norethisterone	A, M
Norinyl-1 (Syntex)	50	1.00	L	norethisterone	A, C, M
Ortho Novin (Ortho-Cilag)	50	1.00	L	norethisterone	M
Ortho Novum 1/50 (Ortho)	50	1.00	L	norethisterone	C, M
Trinordiol (Wyeth)	32	0.09	M	levonorgestrel	A, C, M
Yerminol (Ciba)	40	2.00	n/a	lynestrenol	A, M
Special use – POPs					
Femulen (Searle)		0.50	n/a	ethynodiol diac	A
Micronor (Ortho-Cilag)		0.35	n/a	norethisterone	A, M
Noriday (Syntex)		0.35	n/a	norethisterone	A, M
Post-coital					
Postinor (Medimpex)		0.75	n/a	levonorgestrel	A, C, M, P
Less suitable					
Anovlar 21 (Schering)	50	4.00	H	norethist. acet	P
Conova 30 (Searle)	30	2.00	H	ethynodiol diac	A, C
Eugynon/ED (Schering)	50	0.50	H	norgestrel	A, C, M
Gravistat (Germed)	50	0.13	H	levonorgestrel	M
Loestrin 20 (Parke-Davis)	20	1.00	L	norethist. acet	A, M
Microgynon 30/ED (Schering)	30	0.15	H	levonorgestrel	A, C, M
Neogynon/ED (Schering)	50	0.25	H	levonorgestrel	A, C, M
Nordette (Wyeth)	30	0.15	H	levonorgestrel	A, C, M, P
Nordiol (Wyeth)	50	0.25	H	levonorgestrel	A, C, M
Ortho Novum (Ortho)	100	2.00	n/a	norethisterone	C
Ortho Novum 1/80 (Ortho)	80	1.00	L	norethisterone	C
Ovidon (Medimpex)	50	0.25	H	levonorgestrel	A, M
Ovostat (Organon)	50	1.00	n/a	lynestrenol	A
Ovostat 28 (Organon)	50	1.00	n/a	lynestrenol	A
Ovral (Wyeth)	50	0.50	H	norgestrel	A, C, M, P
Ovulen 50 (Searle)	50	1.00	H	ethynodiol diac	A, C, M
Rigevidon (Medimpex)	30	0.15	H	levonorgestrel	A, M

Key: OES = amount of oestrogen in micrograms; PRO = amount of progestogen in milligrams; PRO POT = progestogen potency, expressed as high (H), medium (M), low (L), or not available (n/a); Availability: A = Africa (29 products), C = Caribbean (25 products), M = Middle East (27 products), P = Pakistan (6 products); Selection/Rating: First choice for prescribing (low oestrogen and low progestogen potency); Second choice (either low oestrogen with medium progestogen potency, or higher oestrogen with low progestogen potency); Special Use: the progestogen-only pills which are recommended for older women or those who suffer strong side effects from pills containing oestrogen; Less suitable = pills that are difficult to recommend, usually because they contain a higher oestrogen level coupled with a high progestogen potency, or are unbalanced, in that the progestogen level is too high

Sources: *MIMS Africa* (July 1991), *MIMS Caribbean* (Jan 1991), *MIMS Middle East* (June 1990), *QIMP* (Pakistan, Mar-Aug 1990)

Recommendations for action

1. Governments should review the oral contraceptives on the market in their countries with a view to reducing the number of products, bearing in mind the overwhelming weight of advice that suggests that low-dose pills are safer.

2. Women should be provided with clear and consistent objective information comparing the advantages and disadvantages of the various methods of contraception available. If a choice is made to use an oral contraceptive, clear instruction about its proper use should be given, including the need for regular medical check ups.

3. Where oral contraceptives are distributed as part of family planning programmes, care should be taken to ensure that adequate equipment and training is available for health workers to be able to perform the necessary tests prior to dispensing, and that follow-up services are available.

4. Manufacturers should stop the production and marketing of high-dose oral contraceptives with an excessive progestogen content.

5. Research should continue into the long-term effects of the use of oral contraceptives, particularly the effect on women who start to take the pill at an early age or take it for many years.

References:

1. Gilman, A.G., Rall, T.W., Nies, A.S., and Taylor, P. (eds), *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, New York, Pergamon Press, (8th edn) 1990, p1402
2. Berer, M., "Contraception", chapter 15 in: Phillips, A., Rakusen, J. (eds) and the Boston Women's Health Collective, *The New Our Bodies, Ourselves* (2nd UK edition), London, Penguin Books, 1989, p290
3. LaCheen, C., "Population control and the pharmaceutical industry", in: McDonnell, K. (ed.), *Adverse Effects: Women and the Pharmaceutical Industry*, Penang, IOCU, 1986, p108
4. Wharton, C. and Blackburn, R., "Lower-dose pills", *Population Reports*, Series A, No 7, Baltimore, Johns Hopkins University, Nov 1988, p1
5. Anon., "OC needs in developing countries", *Scrip*, No 1696, 28 Feb 1992, p21
6. Anon., "Schering AG's prospects", *Scrip*, No 1500, 28 Mar 1990, p10
7. Milne, R. and Vessey, M., "The pill and mortality – an overview", *Journal of Public Health Medicine*, Vol 14, No 1, 1992, pp9-16
8. Anon., "US use of OCs at highest level since 1975", *Scrip*, No 1653, 20 Sep 1991, p28
9. Anon., *The US Market for Selected Products Associated with Fertility & Infertility*, New York, Frost & Sullivan, 1991
10. Anon., "Decline of oral contraceptive use in Mexico", *Scrip*, No 1684, 17 Jan 1992, p20
11. Wharton and Blackburn, 1988, op cit, p12
12. Ibid, p13
13. Finger, W.R., "Using oral contraceptives correctly: progress on package instructions", *Network*, Vol 12, No 2, Sep 1991, pp14-17 and 27; Potter, L.S., "Oral contraceptive compliance and its role in the effectiveness of the method", chapter 16 in: Caramer, J.A. and Spilker, B. (eds), *Patient Compliance in Medical Practice and Clinical Trials*, New York, Raven Press, 1991, pp195-207

13a. Guillebaud, J., *The Pill*, Oxford University Press, (4th edn) 1991, pp58-65 and 209-14

14. Gilmer, M.D.G., "Metabolic effects of combined oral contraceptives", chapter 2 in: Filshie, M. and Guillebaud, J. (eds), *Contraception: Science and Practice*, London, Butterworth-Heinemann, 1989, pp31-2
15. Guillebaud, J., op cit, p70
16. Guillebaud, J., *Contraception: your questions answered*, London, Churchill Livingstone, (revised edn) 1991, pp102-3 and 117
17. Pike, M.C., Henderson, B.E., et al, "Breast cancer in young women and use of oral contraceptives: possible modifying effect of formulation and age at use"; and Vessey, M.P., Lawless, M., et al, "Neoplasia of the cervix uteri and contraception: a possible adverse effect of the pill", *Lancet*, No 8356, 22 Oct 1983, pp926-30 and 930-4
18. UK National Case-control Study Group, "Oral contraceptive use and breast cancer risk in young women", *Lancet*, No 8645, 6 May 1989, pp973-82
19. Romieu, I., Willett, W.C., et al, "Prospective study of oral contraceptive use and risk of breast cancer in women", *Journal of the National Cancer Institute*, Vol 81, No 17, 6 Sep 1989, pp1313-21
20. Wingo, P.A., Lee, N.C., et al, "Age-specific differences in the relationship between oral contraceptive use and breast cancer", *Obstetrics and Gynecology*, Vol 78, No 2, Aug 1991, pp161-70
21. Staffa, J.A., Newschaffer, C.J., et al, "Progestins and breast cancer: an epidemiologic review", *Fertility and Sterility*, Vol 57, No 3, Mar 1992, pp473-91
22. Harlap, S., "Oral contraceptives and breast cancer: cause and effect?", *Journal of Reproductive Medicine*, Vol 36, No 5, May 1991, pp374-95
23. Thomas, D.B., "Oral contraceptives and breast cancer: review of the epidemiologic literature", *Contraception*, Vol 43, No 6, Jun 1991, pp597-642
24. Szarewski, A. and Guillebaud, J., "Contraception: current state of the art", *British Medical Journal*, Vol 302, 25 May 1991, pp1224-6
25. McPherson, K., "Combined progestin and estrogen (oral) and other forms of hormonal contraception", *Current Opinion in Obstetrics and Gynecology*, Vol 3, 1991, pp486-90
26. Djerassi, C., "The bitter pill", *Science*, Vol 245, 28 Jul 1989, pp356-60
27. Vessey, M.P., "Oral contraception and cancer", chapter 4 in: Filshie and Guillebaud, 1989, op cit, p63
28. Thomas, D.B., "The WHO Collaborative Study of Neoplasia and Steroid Contraceptives: the influence of combined oral contraceptives on risk of neoplasms in developing and developed countries", *Contraception*, Vol 43, No 6, June 1991, pp695-710
29. Guillebaud, 1991, *Contraception*, op cit, p43
30. Anon., "Japan's wait for low dose 'pill'", *Lancet*, Vol 339, 4 Apr 1992, p865
31. Guillebaud, 1991, *Contraception*, op cit, p152
32. Vessey, 1989, op cit, pp63-4; Hsing, A.W., Hoover, R.N., et al, "Oral contraceptive use and primary liver cancer among young women", *Cancer Causes and Control*, Vol 3, 1992, pp43-8
33. AMA, *Drug Evaluations*, Philadelphia, W.B. Saunders Co., (6th edn) 1986, p724
34. Parish, P., *Medicines: a guide for everybody*, London, Penguin (6th edn, revised), 1989, p247

34a. BMA and the Royal Pharmaceutical Society of Great Britain, *British National Formulary*, London, BMA and The Pharmaceutical Press, No 23, Mar 1992, pp23\83 and 286

35. Ibid, p240
36. Berer, 1989, op cit, p292
37. Dnfe, J., "Complications of combined oral contraception", chapter 3 in: Filshie and Guillebaud, 1989, op cit, p45
38. Petitti, D.B. and Porterfield, D., "Worldwide variations in the lifetime probability of reproductive cancer in women: implications of best-case, worst-case and likely-case assumptions about the effect of oral contraceptive use", *Contraception*, Vol 45, No 2, Feb 1992, pp93-104
39. Mishell Jr, D.R., "Contraception", *New England Journal of Medicine*, Vol 320, No 12, 23 Mar 1989, pp777-87
40. Parish, 1989, op cit, p247
41. Guillebaud, 1991, *Contraception*, op cit, p120
42. AMA, 1986, op cit, p720
43. Mishell, 1989, op cit, pp777-87
44. Anon., "FDA warns OC manufacturers", *Scrip*, No 1630, 3 Jul 1991, p18
45. von Eickstedt, K.-W., "Sex hormones and related compounds including hormonal contraceptives", chapter 42 in: Dukes, M.N.G. and Beeley, L., (eds), *Side Effects of Drugs Annual 14*, Amsterdam, Elsevier, 1990, p349
46. BMA and the Royal Pharmaceutical Society of Great Britain, 1992, op cit, p285
47. Guillebaud, 1991, *The Pill*, op cit, p222

47a. Lewis, P.J. and Hurden, E.L., "Breast feeding and drug treatment", in Hawkins, D.F. (ed.), *Drugs and Pregnancy*, London, Churchill Livingstone, (2nd edn) 1987, pp304-32

48. Gilman, Rall, et al, 1990, op cit, p1409
49. AMA, 1986, op cit, p723
50. LaCheen, 1986, op cit, p108
51. Guillebaud, 1991, *Contraception*, op cit, p127
52. BMA and the Royal Pharmaceutical Society of Great Britain, 1992, op cit, p284
53. Wharton, Blackburn, 1988, op cit, p9

Chetley, A. *Problem Drugs*, Amsterdam,
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8C. IUDs

Effective... but safe?

Rosalind Hunt had an intrauterine device (IUD) fitted in the days when doctors, encouraged by promotion from manufacturers, thought it was a "good option" for women who had not had children. Rosalind subsequently developed a painful infection in her uterus which was treated with antibiotics. She also had the IUD removed. When she later married and tried to have children, she discovered that the infection had left her infertile – her Fallopian tubes were blocked with scar tissue. She says of the IUD, "it was a device promoted for people like me who had not had children but we were not adequately informed of the risks we were taking".[1]

Rosalind Hunt lives in England, where there is relatively easy access to health care. Elvia Alvarado lives in a rural area of Honduras and tells a different story:
"Methods like the IUD give lots of infections. And you have to remember that when we get sick it's hard for us to get to a doctor. The nearest clinic is far away. And even if we could see a doctor, we can't afford to buy the medicine. I know a woman who had to pay $60 to get rid of an infection in her vagina. That's more than most of us make in a month!"[2]

The IUD is one of the most widely used contraceptive methods with more than 80 million users worldwide, nearly 60 million of them in the People's Republic of China.[3] Concern about the risk of infertility has led to a decline in IUD use in industrialised countries in recent years. An estimated 6% of women in the USA and Europe use an IUD.[4] In the UK, the actual number using an IUD is estimated at about 500,000 or some 8% of women using contraception. This makes IUDs the third most popular method in the UK (after condoms and the pill).[5] In the USA in 1988, an estimated 700,000 women used the IUD (down from more than 2.2 million in 1982),[6] or about 3% of women using contraception.[7]

How IUDs work

IUDs are either inert, copper-bearing or hormone-releasing plastic or metal devices inserted into the uterus. How they act is not absolutely certain, but it is thought that they inhibit sperm and egg movement and inhibit fertilisation.[8] The current theory is that the IUD causes a sterile inflammatory reaction in the uterus so that the sperm or fertilised egg are rendered ineffective by white blood cells. Copper is also toxic to sperm and may have other effects which interfere with conception, so this may be a factor in IUDs containing copper. The hormone-releasing IUDs alter hormonal activity in the uterus and also make the cervical mucus less permeable to sperm.[9]

Effectiveness

The IUD is highly effective. Pregnancy rates for women with IUDs range from 1 to 4% each year.[10] These failure rates are generally lower than failure rates with barrier methods, which have the advantage of fewer adverse effects. Unlike oral contraceptives, the non-hormonal IUDs do not have systemic metabolic effects and thus can be used by women who cannot use oral contraceptives because of age,

cigarette smoking, or certain pre-existing diseases, such as hypertension. Continuation rates with IUDs tend to be higher than many other forms of contraception due, at least in part, to the need to have a trained health worker to remove the device. One factor which can interfere with continuation and with the effectiveness of the method is expulsion of the device, since the uterus tends to expel foreign bodies. Rates of expulsion range from one to almost 20 per 100 users, depending on the shape and design of the IUD.[11]

If pregnancy occurs with an IUD in place, the risk (up to 50%) of spontaneous abortion is greater than without an IUD; premature delivery and stillbirth may also be more common. Ectopic pregnancy – when the embryo becomes implanted in one of the fallopian tubes rather than the uterus – is more common among women who become pregnant when wearing an IUD than without an IUD; its incidence is somewhere between one in 20 and one in 30 pregnancies, compared to about one in 200 pregnancies among non-IUD users.[12] Because of the risks to both the fetus and the mother, the IUD should be removed as soon as pregnancy is diagnosed. If this cannot be done (because the tail of the device is not visible) the World Health Organization (WHO) says that the woman "should be carefully counselled about the risks of continuing the pregnancy.... If a woman continues her pregnancy with an IUD in place, special obstetric care is necessary because of an increased risk of premature birth and a decreased likelihood of a live birth."[13]

Adverse effects

The most common adverse effect of the IUD is increased blood loss – heavy or prolonged periods, intermenstrual bleeding or spotting – often accompanied by pain and discomfort, and a discharge, either watery or mucoid. This is also the commonest reason for discontinuing the use of an IUD.[14] A less frequent but more severe adverse effect is perforation of the uterus, which occurs in about one per 1000 insertions, almost always at the time of insertion.[15]

Pelvic inflammatory disease

Another serious complication associated with IUD use is pelvic inflammatory disease (PID). Although all IUDs have been linked with PID, one in particular – the Dalkon Shield – was found to be especially hazardous. A large-scale study carried out in 1983 found that the Dalkon Shield carried at least a five-fold risk of PID compared with all the other IUDs in use.[16] (See the box on the Dalkon Shield.)

PID is an infection within the fallopian tubes, ovaries, or uterus. Its main symptoms are severe pain or tenderness of the lower abdomen, discharge (sometimes bloody) from the vagina, and fever. An indication of the seriousness and prevalence of acute PID is that it develops in an estimated 1% of young

The Dalkon Shield

Made of plastic, the Dalkon Shield was oval in shape, with small fins extending from its right and left sides, and a tail string to facilitate proper placement and removal. It was developed in the late 1960s and originally marketed by the Dalkon Corporation, which sold about 27,000 of these IUDs. In June 1970, A H Robins acquired the product from the Dalkon Corporation and began sales and distribution in January 1971.

Between 1971 and 1974, about 2.8 million Dalkon Shields were distributed in the USA and about 1.7 million in other countries, including about 700,000 through the US Agency for International Development (USAID). The company estimates that 2.2 million Dalkon Shields were actually used in the USA and less than 1.4 million were actually used outside the USA.

The Dalkon Shield was promoted by A H Robins as "the first IUD specifically designed for women who had not yet had children". However problems soon began to develop, caused primarily by the tail of the device. (Many IUDs have a tail which enables users to check whether the device is still in place.) Unlike other IUDs, the tail of the Dalkon Shield was made up of several filaments enclosed in a sheath. Experiments later showed that this tail acted like a "wick" giving bacteria easy access to the uterus.

The result was serious PID for thousands of women, sterility, and for at least 18 women, death. In 1973, Robins began talks with the US Food and Drug Administration (FDA) on the safety of the product. In June 1974, Robins withdrew the Dalkon Shield from the US market pending further study of it and other IUDs. In December 1974, the FDA completed its study and said that the product could be marketed again with a modified tail string under a special patient registry system. Robins, however, chose not to remarket it. Sales were discontinued outside the USA between July 1974 and March 1975.

A series of lawsuits was launched by women harmed by the Dalkon Shield and at least $500 million was paid out in damages before Robins filed for protective bankruptcy in August 1985. In January 1986, the company held simultaneous press conferences in 20 major cities in an attempt to reach all four million Dalkon Shield users in 92 countries with the message that if they wanted to claim for damages, they had to submit such a claim by 30 April 1986. Approximately 192,000 claims were filed, most of which were in the USA, where the company carried out the most extensive publicity. A trust fund was set up with more than $2,300 million to settle the claims.

Sources: A H Robins (Canada), *The Dalkon Shield – Background*, information for the press, undated (late 1985/early 1986); Pappert, A., "The rise and fall of the IUD", in: McDonnell, K. (ed.), *Adverse Effects: Women and the Pharmaceutical Industry*, Penang, IOCU, 1986, p169; Tatum, H.J. and Connell, E.B., "Intrauterine contraceptive devices", chapter 9 in: Filshie, M. and Guillebaud, J. (eds), *Contraception: Science and Practice*, London, Butterworth-Heinemann, 1989, p156; Dyer, C., "Hospital records blocked in Dalkon Shield claims", *Sunday Times*, 13 Apr 1986; Anon., "Dalkon Shield Trust settlement terms", *Scrip*, No 1504, 11 Apr 1990, p27

use of an IUD may increase a woman's risk of HIV infection. According to a large European study, among women with male HIV-positive sexual partners, those who were using an IUD for contraception had the highest rate (40%) of HIV infection.[25]

Different types of IUDs

The most widely used IUD is the inert Ota ring device which is prevalent in China. In the rest of the world, copper-bearing devices are the favoured types, but recently some hormone-releasing devices have been tested. These offer both advantages and disadvantages. The main advantages of the latest type of IUD – a device which releases 20 micrograms of the progestogen levonorgestrel per day – are low rates of pregnancy and possibly lowered incidence of PID. The disadvantages include hormonal side effects and bleeding disturbances, including absence of menstrual periods.[26] The other hormone-releasing IUD – Progestasert – has been found to increase the absolute risk of ectopic pregnancy by 1.5-1.8 times.[27]

There are no simple rules to the choice of device. As long as there is no sensitivity to copper, any of the copper-bearing IUDs could be used. A prime consideration in developing countries, however, is the lack of access to adequate health care facilities for regular check-ups and for removal and replacement. Because the non-hormonal IUDs can cause heavy menstrual bleeding, their use in women prone to anaemia may not be advisable. Research is inadequate to determine whether hormonal IUDs offer particular advantages for women with anaemia.

Research into new IUDs has been hit by the backlash that resulted from the litigation over the Dalkon Shield and later lawsuits against another US manufacturer, G.D. Searle – maker of the Cu-7 and the Tatum-T IUDs. At the end of January 1986, G.D. Searle announced that it was withdrawing from the US IUD market "because of the cost of defending the products against lawsuits and the company's inability to obtain adequate insurance". Cu-7 was the most frequently prescribed IUD in the USA. Searle estimated that about one million of the two devices were in use in the USA and defended their "safety, efficacy and medical utility". The devices have been the subject of 775 lawsuits against Searle during the 12 years they were on the market in the USA.[28] Only 20 cases have gone to a full trial (Searle won 16), and more than 450 suits were settled out of court. Some 300 are still pending.[29] Nearly 200 women in New Zealand and more than 200 women in Australia also filed suits against the company.[30]

Not for everyone

Although most people agree with the WHO that the IUD is "an important method of fertility regulation" for women in both developed and developing countries,[31] it is not suitable for all women. Women who have not completed their desired family size, who have had an ectopic pregnancy, who have or whose partners have multiple sexual partners, are not suitable candidates for an IUD.[32] The IUD should be avoided in women with current pelvic infection, known or suspected pregnancy, a distorted uterine cavity, undiagnosed abnormal vaginal bleeding, suspected malignancy of the genital tract, or known infection with human immunodeficiency virus (HIV). Copper allergy is a contraindication to copper-carrying devices. Relative contraindications include a past history of pelvic infection, valvular heart disease with the risk of subacute bacterial endocarditis, uterine scars, anaemia and fibroids.[33] One expert notes that the IUD "is especially suitable for women who have completed their families and have contraindications to the use of oral contraceptives".[34]

Women who do use an IUD should be informed what type of device it is, told how to check that it is still in place, be advised to return to the clinic for an initial examination within one to three months after insertion and thereafter annually, and be told what side effects to expect. They should also be told what to do in case of severe adverse effects such as PID or perforation of the uterus.[35] Before attempting insertions of IUDs, clinicians should receive practical lessons from someone with experience and be given a chance to practice insertion using a small plastic model.[36]

Recommendations for action

1. Restrict the use of IUDs to women over 30 who have already had children,[37] or to younger women only when they are certain they no longer want children.
2. Ensure that any woman who uses an IUD is first given full information about the possible risks. It is particularly important that women who have not yet had a child should be clearly warned of the possibility of infertility and encouraged to choose an alternative method of contraception.
3. Ensure that no woman is fitted with an IUD unless a detailed medical history is taken and tests for vaginal and cervical infections (including chlamydia and gonorrhoea) are carried out prior to insertion; unless the device is inserted by a well-trained health worker; and unless she has access to removal on request and to appropriate follow-up care if PID develops. Women should be informed about the signs of PID and uterine perforation and be encouraged to seek immediate medical attention if a complication develops.

women annually and causes more illness in women of 15-25 years of age than all other serious infections combined. Worldwide, PID is a leading cause of infertility. In the USA, the disease is responsible for between five and 20% of all hospital admissions for gynaecological problems[17] and the cost of treating PID and its consequent illnesses is estimated at $3.5 billion a year.[18] More than one million women in the USA suffer from PID every year.[19]

The link between PID and IUDs is "one of the most controversial topics in contemporary contraception", despite extensive research worldwide. Most studies have found an increased risk of PID among IUD users, in some cases up to nine times. However, the most objective studies put the range of risk at between 1.5 and 2.6 times. Closer examination of the data suggests that the risk is greatest near the time of insertion of the device.[20] A recent study carried out by WHO's Special Programme of Research, Development and Research Training in Human Reproduction confirmed that the risk of PID was greatest closest to the time of insertion – in this case, six times more likely during the first 20 days. The study also found that the highest risks were among women who had not previously had children, those who were the youngest (15 to 24 years of age), or those who lived in Africa.[21]

No one is certain why women using IUDs are more susceptible to PID. The association of the highest risk with the time of insertion, however, suggests that bacteria may be introduced during the insertion process.[22] Another factor seems to be the risk of acquiring sexually transmitted diseases (STDs). Chlamydia, one of the most common STDs, is asymptomatic in three out of four infected women. If a woman infected with chlamydia or another STD has an IUD inserted, the infection can spread and cause PID.[22a] Women at low risk of acquiring STDs have little increased risk of IUD-associated PID.[23] As a result of recent studies, it now becomes apparent that women who have a high risk of PID – which includes those with a previous history of PID, women under 25 who do not have children, and all women who have or whose partners have multiple sexual partners – should use a different form of contraception.[24]

IUDs and AIDS

The relationship between IUDs and STDs should also cause concern in settings where the spread of human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS) is prevalent. The IUD does not offer any protection against HIV transmission. Indeed, there is some evidence to suggest that the

Table 8C-1
Comparison of different types of IUDs

Device	Manufacturer	Country	Maximum Duration[1] (years)	Pregnancy Rate[2] /100	Continuation Rate[2] /100
Copper-bearing					
Lippes Loop Cu200	Ortho US	USA	10(?)	1.2	74.2
T Cu 200 Ag	Outokumpu Oy	Finland	6	5.6	50.0
T Cu 220 C	Ortho Canada	Canada	15–20	1.8	59.7
	Outokumpu Oy	Finland			
T Cu 380A	Ortho Canada	Canada	6	1.0	50.1
	GynoMed	USA	4		
T Cu 380Ag	Outokumpu Oy	Finland	10–15		
Nova T	Outokumpu Oy	Finland	6	1.8	51.6
	Leiras	Finland			
Multiload Cu 250	Multilan	Switz.	4	1.1–2.5	74.0–89.5
Multiload Cu 375	Multilan	Switz.	5	0.9	65.6
Progestogen-bearing					
Progestasert (progesterone)	Alza	USA	1	1.9	n.a.
LNG T (levonorgestrel)	Leiras	Finland	6(?)[3]	0.1	75.3

Notes:
1. Maximum duration is a probable or theoretical figure; for the copper-bearing devices, the usual proven duration is accepted at between three to five years
2. Pregnancy and continuation rates are both after two years, both per 100 women users
3. Not in widespread use yet

Sources: Lippes data from: Randic, L., et al, "The effect of adding copper onto Lippes Loop IUDs: results from a ten-year study in Yugoslavia", *Contraception*, Vol 43, No 3, Mar 1991, pp229-39; other data on copper-bearing devices from: Tatum, H.J. and Connell, E.B., "Intrauterine contraceptive devices", chapter 9 in: Filshie, M. and Guillebaud, J. (eds), *Contraception: Science and Practice*, London, Butterworth-Heinemann, 1989, pp148 and 164; data on Progestasert from: Sivin, I., "Dose- and age-dependent ectopic pregnancy rates with intrauterine contraception", *Obstetrics and Gynecology*, Vol 78, No 2, Aug 1991, pp291-8; data on LNG T from: Sivin, I., Stern, J., et al, "Prolonged intrauterine contraception: a seven-year randomized study of the levonorgestrel 20mcg/day (LNg 20) and the copper T380 Ag IUDs", *Contraception*, Vol 44, No 5, Nov 1991, pp473-80

References:

1. Pownall, M., "Fears and lawsuits give IUDs an uncertain future", *The Independent*, 2 Dec 1986
2. Lappé, F.M. and Schurman, R., *Taking Population Seriously*, London, Earthscan Publications, 1989, p48
3. Farley, T.M.M., Rosenberg, M.J., et al, "Intrauterine devices and pelvic inflammatory disease: an international perspective", *Lancet*, Vol 339, No 8796, 28 Mar 1992, pp785-8
4. MacKenzie, D., "World Health Organisation supports the IUD", *New Scientist*, 12 Nov 1987, p35
5. Berer, M., "Contraception", chapter 15 in: Phillips, A., Rakusen, J. (eds) and the Boston Women's Health Collective, *The New Our Bodies, Ourselves* (2nd UK edition), London, Penguin Books, 1989, p287
6. Farley, Rosenberg, et al, 1992, op cit, pp785-8
7. Graedon, J. and Graedon, T., *Graedon's Best Medicine: from herbal remedies to high-tech Rx breakthrough*, New York, Bantam Books, 1991, p352
8. WHO, *Mechanism of Action, Safety and Efficacy of Intrauterine Devices*, Technical Report Series No 753, Geneva, WHO, 1987, p68
9. Tatum, H.J. and Connell, E.B., "Intrauterine contraceptive devices", chapter 9 in: Filshie, M. and Guillebaud, J. (eds), *Contraception: Science and Practice*, London, Butterworth-Heinemann, 1989, pp146-7
10. Berer, 1989, op cit, p289
11. Tatum and Connell, 1989, op cit, pp150-1
12. Guillebaud, J., *Contraception: your questions answered*, London, Churchill Livingstone, (revised edn) 1991, pp213-4, 222
13. WHO, 1987, op cit, pp49-51
14. Anon., "Does infection occur with modern intrauterine devices?", *Lancet*, Vol 339, No 8796, 28 Mar 1992, pp783-4
15. WHO, 1987, op cit, p46
16. Tatum and Connell, 1989, op cit, p157
17. Bumakis, T.G. and Hildebrandt, N.B.; "Pelvic inflammatory disease: a review with emphasis on antibiotic therapy", *Reviews of Infectious Diseases*, Vol 8, No 1, Jan-Feb 1986, pp86-116
18. Peterson, H.B., Galaid, E.I. and Cates Jr., W., "Pelvic inflammatory disease", *Medical Clinics of North America*, Vol 74, No 6, Nov 1990, pp1603-15
19. Washington, A.E., Cates Jr., W. and Wasserheit, J.N., "Preventing pelvic inflammatory disease", *Journal of the American Medical Association*, Vol 266, No 18, 13 Nov 1991, pp2574-80
20. Washington, A.E., Aral, S.O., et al, "Assessing risk for pelvic inflammatory disease and its sequelae", *Journal of the American Medical Association*, Vol 266, No 18, 13 Nov 1991, pp2581-6
21. Farley, Rosenberg, et al, 1992, op cit, pp785-8
22. Mishell, D.R., "Contraception", *New England Journal of Medicine*, Vol 320, No 12, 23 Mar 1989, pp777-87

22a. Jacobson, J.L., *Women's Reproductive Health: the silent emergency*, (Worldwatch Paper 102), Washington, Worldwatch Institute, 1991, p27 and 33

23. Washington, Aral, et al, 1991, op cit, pp2581-6; Farley, Rosenberg, et al, 1992, op cit, pp785-8
24. Mishell, 1989, op cit, pp777-87
25. European Study Group, "Risk factors for male to female transmission of HIV, *British Medical Journal*, Vol 298, 1989, pp411-15
26. Toivonen, J., Luukkainen, T. and Allonen, H., "Protective effect of intrauterine release of levonorgestrel on pelvic infection- three years' comparative experience of levonorgestrel- and copper-releasing intrauterine devices", *Obstetrics and Gynecology*, Vol 77, No 2, Feb 1991, pp261-4
27. Sivin, I., "Dose- and age-dependent ectopic pregnancy rates with intrauterine contraception", *Obstetrics and Gynecology*, Vol 78, No 2, Aug 1991, pp291-8
28. Anon., "Searle to End Sale of IUDs in US", *International Herald Tribune*, 1/2 Feb 1986
29. Anon., "Searle favoured in latest US Cu-7 trial", *Scrip*, No 1497, 16 Mar 1990, p13
30. Anon., "IUD law suits in New Zealand/Australia", *Scrip*, No 1648, 4 Sep 1991, p11
31. WHO, 1987, op cit, p71
32. Tatum and Connell, 1989, op cit, p160
33. Guillebaud, 1991, op cit, pp231-3
34. Mishell, 1989, op cit, pp777-87
35. Tatum and Connell, 1989, op cit, pp162-3
36. Guillebaud, 1991, op cit, p241
37. Makkonen, K. and Hemminki, E., "Different contraceptive practices: use of contraceptives in Finland and other Nordic countries in the 1970s and 1980s", *Scandinavian Journal of Social Medicine*, Vol 19, No 1, 1991, pp32-8

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Not the first choice

"Long-acting hormonal contraceptives produce an almost invariable disturbance of the menstrual cycle and this may be a source of major concern to the woman."[1]

Contraceptive methods such as injectables which cause menstrual disruption are problematic in many societies because bleeding interferes with praying, fasting, sexual intercourse, and a woman's feeling of health and well-being.[2] There is also uncertainty about the long-term safety of injectable contraceptives. Despite these difficulties, injectables play a large role in family planning programmes in developing countries.

The two major products are progestogens – synthetic hormones modeled on the natural female hormone progesterone. The leading product, depot medroxyprogesterone acetate (Depo-Provera or DMPA), is manufactured by the American company, Upjohn, while the German company, Schering, produces norethisterone oenanthate (Norigest, Noristerat or NET-OEN).

Neither product is widely used as a contraceptive in industrialised countries.[3] For example, because of safety concerns, DMPA was only approved for contraceptive use by the US Food and Drug Administration (FDA) in October 1992 – nearly 20 years after Upjohn first applied for a licence.[4] DMPA is available as a contraceptive in over 90 countries around the world, and NET-OEN is marketed as a contraceptive in over 40 countries.[5] The World Health Organization (WHO) estimates that over 30 million women worldwide have used injectable contraceptives and that about six million women are currently using them.[6] An estimated four million use DMPA,[7] and about one million use NET-OEN.[8] Locally produced brands in China and Latin America account for the remaining usage. In addition, clinical trials are underway in several developing countries to test different versions of a monthly injectable which contains both a progestogen and oestrogen.[9]

The first injectable progestogens were developed in 1953 by Karl Junkmann. In 1957, Junkmann and his associates at Schering produced NET-OEN, and the company began clinical trials. At about the same time, Upjohn developed DMPA and began clinical trials in 1963. The first major field trials for NET-OEN were conducted in Peru and in 1967, Norigest went on the market in Peru. It was withdrawn in 1971 and field trials were suspended after pituitary and breast nodules were found in rats given Norigest. However, family planning researchers concluded that the findings in rats were not applicable to humans,[10] and NET-OEN went back on the market. In 1981, WHO's Toxicology Review Panel concluded that it was safe to introduce NET-OEN into family planning programmes.[11]

DMPA has a similar history. Early animal studies found breast cancer in beagles and endometrial cancer in rhesus monkeys. However, once again, researchers concluded that the animal studies were not applicable to humans, and in 1978, WHO noted that "the available evidence does not indicate a risk of adverse effects associated with Depo-Provera which would preclude the use of this drug as a contraceptive."[12]

Nonetheless, there are still concerns. In most cases, if a carcinogenic effect is demonstrated in any one species, particularly in an organ likely to be affected by the drug, "this is considered to constitute evidence of lack of safety. If a drug is found to produce cancer in more than one species, the strength of the evidence is increased."[13]

How injectables work

Both injectables inhibit the production of hormones by the pituitary gland, which in turn prevents ovulation. Studies also suggest that both drugs have an effect on the production of cervical mucus, on the

fallopian tubes, and on the lining of the uterus, all of which are assumed to play a role in reducing fertility.[14]

The major difference between the two injectables is the duration of contraceptive effect. DMPA is released into the blood stream more slowly than NET-OEN, and usually remains in the body longer. NET-OEN is usually undetectable in the blood by about 70 days after injection and its contraceptive effect is thought to wear off by two to three months, whereas DMPA is often still detectable in the body up to nine months after injection, although the contraceptive effect is thought to wear off by three to four months.[15]

The effectiveness of the two drugs in preventing pregnancy is roughly the same. With DMPA the rate of pregnancy ranges from 0 to 1 per 100 women-years, and for NET-OEN from 0.01 to 1.3 per 100 women-years.[16] Generally, this means that injectables are more effective than oral contraceptives.[17]

Side effects

The most common side effects and the main reason for discontinuation of injectables are disturbances in the menstrual cycle. A leading gynaecologist says that with injectables, the "disturbance of menstruation is so marked and variable, both between patients and within the same woman over time, that it has been called 'menstrual chaos'."[18]

This menstrual chaos can take two forms: either an absence of bleeding (amenorrhoea), or frequent bleeding or spotting. DMPA causes amenorrhoea of more than 90 days duration in up to 40% of women during the first year of use. NET-OEN causes less amenorrhoea, but the incidence of other types of menstrual disturbance is similar to DMPA.[19]

Generally, 30 to 50% of women stop using injectables during the first year.[20] WHO says the reason in one-quarter to one-half of cases is because of menstrual disturbances.[21]

WHO maintains that neither amenorrhoea nor frequent bleeding – providing it is not heavy – are likely to pose any health problems for women. However, WHO does point out that "menstrual irregularity interferes with daily life and for sociocultural reasons is totally unacceptable in some settings."[22]

This is an important point. Even if the *direct* health consequences are not considered severe, a woman who finds the disruption in the menstrual cycle intolerable has little choice but to live with it, for once the injection is given, she will have to wait until the effect wears off. At least in the case of DMPA, there is evidence that although the contraceptive effect may end within about four months of an injection, the side effects can be more long-lasting. The Coordinating Group on Depo-Provera in the UK documented many cases of women suffering bleeding irregularities for several months after a single injection.[23]

Other reported side effects include headaches, weight gain, dizziness, abdominal discomfort, mood changes, and loss of libido. There is also some evidence that the use of DMPA contributes to reductions in bone density and therefore that it should be considered a potential risk factor for osteoporosis.[24] This is especially of concern for long-term users and women at risk for other reasons.

Advantages and disadvantages

The advantages of injectable contraceptives fall into two categories: advantages to the administrators and advantages to the users. In the first case, injectables are seen as effective, convenient, easy to administer and reversible. The early history of injectable contraceptive use is full of incidents where women were simply "processed" in little more than a minute,[25] or where women were not informed about the nature of the injection.[26] Some of this abuse seems to be continuing. There were reports that in East Timor in 1989, as a way of controlling the local population, adolescents were being injected with contraceptives without their knowledge or consent.[27]

From the point of view of a woman seeking contraception, the major advantages reported are effectiveness, convenience, freedom from the fear of forgetting to take precautions, the ease of administration and the fact that "it remains a woman's secret"[28] and partners cannot interfere with its use. This last factor can be very important to women in repressive cultural and family situations.

An important factor in the acceptance of injectable contraceptives is undoubtedly the widespread (but untrue) belief that medicines given by injection are more powerful and more effective than medicines taken orally.[29]

A possible cancer risk?

The most prominent disadvantage is menstrual disruption. Another concern is that "there is not enough evidence to provide clear assurances concerning any long-term risks of injectables".[30] The possible risk of cancer associated with the use of injectables is the most serious of these doubts.

WHO undertook an extensive research project in 11 countries to examine the relationship between the use of steroid contraceptives including DMPA and NET-OEN and the development of cancer. WHO concluded that there was no indication of an increased risk of cancer of the breast, womb, ovary or liver in women using DMPA.[31] It also added that there was no evidence of any increased risk of cervical

cancer, although a multi-country study reported in 1984 *did* show a doubling of risk of cervical cancer in women who used DMPA for five or more years.[32] There may be other causative factors such as the sexual activity of the women's partners or their own smoking practices. Another WHO study in five centres to assess breast cancer risks found that risk did increase within the first four years of initial use, particularly among women under 35 years of age. Despite this finding, the report of the study concluded that "women who have used DMPA for a long time and who initiated use many years previously are not at increased risk of breast cancer.[33] One gynaecologist has concluded that "there is no evidence" that injectables cause cancer, "nor proof of the reverse".[34]

A concern with all systemic contraceptives is the possible effect on the later development of infants who are exposed in utero as a result of contraceptive failure or the initiation of contraception in a woman with undiagnosed pregnancy. The human evidence available on the effect of injectables on the fetus is difficult to evaluate, primarily because of a lack of large-scale studies. However, progestogens have been associated with birth defects in both humans and animals. Two recent cohort studies in Thailand found that early, high-dose in utero exposure to DMPA can lead to low birth weight, and to an increase in infant mortality.[35]

A disadvantage that has become more important in recent years is the possible risk of AIDS as the result of the human immunodeficiency virus having been transmitted via injections given with unsterilised syringes. As WHO points out, "in many countries, the sterilisation of needles and syringes by health workers is not always satisfactory".[36]

Contraindications and cautions

Special care should be taken in the use of injectables. They are not first choice contraceptives. According to WHO, the contraindications to the use of injectables are:

- cancer of the breast or an undiagnosed breast lump;
- active viral hepatitis A;
- cardiovascular disorders;
- coagulation or lipid disorders;
- undiagnosed abnormal uterine bleeding or other symptoms of possible genital cancer;
- pre-existing or suspected pregnancy; and no earlier than six weeks after delivery.[37]

If injectables are used by breastfeeding women, their babies receive small amounts of progestogens in the milk. This has led to concern that progestogens might have an adverse effect on neonatal growth or subsequent development.[38]

WHO also notes that the use of injectable contraceptives should be avoided if possible among young adolescents and women over 40. This advice is due to the lack of firm scientific information assuring safety. With young adolescents, "caution is usually advised if any hormonal method is prescribed within the first 2 years after the menarche" (start of menstruation) because the effects of administering hormonal contraceptives on later sexual development and reproductive function "are not fully understood".

For women over 40, the use of any hormonal contraceptive can mask the start of the menopause. With injectables, the disturbances in the menstrual cycle may be mistaken for signs of the menopause and contraception may be stopped prematurely. Also, irregular bleeding in woman of this age may be a sign of underlying gynaecological disease which should be investigated.

In addition, WHO lists several "special problems" where great care in the use of injectables should be taken. These include abnormal liver function or recent history of liver disease, and diabetes mellitus or history of gestational diabetes.[39]

Controls necessary for proper use

A major conclusion about the use of any injectable contraceptive is that, with many questions still unanswered, caution should be used in administration, and great care should be taken in preparing women for its use and in detailed follow-up as to its effects.

The woman, preferably with her partner, should be informed of the various contraceptive methods available, and the risks and benefits of each method should be clearly explained. Once the woman has made her choice, counselling should provide accurate information about how the method works, known contraindications, side effects to expect, and a reminder that she is welcome to return to the clinic at any time to discuss problems and any doubts that may arise. With injectables, she should also be told that it may be six months or more after the time of the last injection before her fertility returns.

A detailed medical history and physical examination are needed to provide information on age, menstrual history, obstetrical history, and any history of jaundice or other liver disease, cardiovascular disease or diabetes. Regular follow-up, including annual pelvic and breast examinations and a cervical smear, is also recommended.[40]

There are, of course, problems with suggesting that injectable contraceptives should only be used in controlled situations with adequate follow-up. This requires carefully designed family planning programmes with well-trained staff who are not assessed on their efficiency – "processing" a pre-set number of women per day, month or year – but on their ability to provide adequate, objective counselling and

support for women who come to them for advice. Tight control is also needed over the distribution of injectable contraceptives to prevent them becoming available for purchase without a prescription or examination.

The likelihood of such controls being in place in developing countries is remote. That, combined with deficiencies in the basic health infrastructure in many countries has to cast a serious shadow of doubt on the suitability of injectable contraceptives. In 1982, the Swedish International Development Authority (SIDA), adopted a formal policy against supplying DMPA. A SIDA official said the reason for the decision "was not medical but the fact that it would be difficult and expensive to control its proper use in rural areas in developing countries".[41]

Many questions about safety and assurance of informed consent remain unanswered. While some health workers and the pharmaceutical companies involved argue that there are no reasons to worry about the widespread introduction of injectables, other health workers, women's groups, consumer groups and some governments have found ample cause for worry.

Recommendations for action

1. If injectables cannot be provided safely and respectfully and with a woman's fully informed choice, they should not be provided.
2. This means acknowledging that injectables are not first choice contraceptives and removing them from the *regular* pharmaceutical market, restricting their availability and use to those settings where conditions for safe use can be met.
3. Any woman considering the use of an injectable contraceptive should have been fully informed about alternative methods, about the benefits and side effects of injectables, and given time to consider her choice.
4. If an injectable is chosen, the woman should be carefully examined for any possible contraindications, and after receiving the injection, should be followed up to monitor any adverse effects and take steps to minimise those effects.
5. Further research is needed on injectables to better evaluate their long-term safety.
6. Research efforts need to be expanded to improve the availability and convenience of existing user-controlled methods of contraception including barrier methods.

References

1. Fraser, I.S., "Systemic hormonal contraception by non-oral routes", chapter 7 in: Filshie, M. and Guillebaud, J. (eds), *Contraception: Science and Practice*, London, Butterworth-Heinemann, 1989, p117
2. WHO, *Creating Common Ground: Women's Perspectives on the Selection and Introduction of Fertility Regulation Technologies*, WHO/HRP/IIT/91, Geneva, WHO, 1991, p25
3. Berer, M., "Contraception", chapter 15 in: Phillips, A., Rakusen, J. (eds) and the Boston Women's Health Collective, *The New Our Bodies, Ourselves* (2nd UK edition), London, Penguin Books, 1989, p296
4. Anon., "Depo-Provera approved in the US", *Scrip*, No 1768, 6 Nov 1992, p19
5. Fraser, op cit, p113
6. WHO, *Injectable Contraceptives*, Geneva, WHO, 1990. p2
7. Hardon, A., "Contraceptive research: women's perspectives", chapter 2 in: Mintzes, B. (ed.), *A Question of Control: Women's Perspectives on the Development and Use of Contraceptive Technologies*, Amsterdam, WEMOS Women and Pharmaceuticals Project/HAI, 1992, p12
8. Anon., "Long-acting steroids provide new options", *Network*, Vol 9, No 3, Spring 1988, p2
9. Khanna, J., van Look, P.F.A., and Griffin, P.D. (eds), *Reproductive Health: a Key to a Brighter Future*. Geneva, WHO, 1992, p89
10. Rinehart, W. and Winter, J., "Injectable progestogens – officials debate but use increases", *Population Reports*, Series K, No 1, March 1975, ppK1-K16
11. WHO, 1990, op cit, pp5-6
12. Ibid, p5
13. Coney, S., "A living laboratory: The New Zealand connection in the marketing of Depo-Provera", in: Davis, P. (ed.), *For Health or Profit? Medicine, the Pharmaceutical Industry and the State in New Zealand*, Auckland, Oxford University Press, 1992, p119-43
14. WHO, 1990, op cit, pp4-5; Guillebaud, J., *Contraception: your questions answered*, London, Churchill Livingstone, (revised edn) 1991, p185
15. WHO, *Facts about injectable contraceptives*, Geneva, Special Programme of Research Development and Research Training in Human Reproduction, 1982. (Reprinted from: *Bulletin of the World Health Organisation*, 60(2): 1982, pp199-210)
16. Guillebaud, op cit, p186
17. WHO, 1990, op cit, p20
18. Guillebaud, op cit, p189
19. Fraser, op cit, p117
20. Hardon, op cit, p12
21. WHO, 1990, op cit, p12
22. Khanna, et al, op cit, p89
23. Berer, op cit, p298
24. Cundy, T., Evans, M., et al, "Bone density in women receiving depot medroxyprogesterone acetate for contraception", *British Medical Journal*, Vol 303, 6 Jul 1991, pp13-16
25. Rinehart and Winter, op cit, ppK1-K16
26. LaCheen, C., "Population control and the pharmaceutical industry", in: McDonnell, K. (ed.), *Adverse Effects: Women and the Pharmaceutical Industry* Penang, IOCU, 1986, p120
27. Vittachi, A., "The healer myth", *New Internationalist*, Sep 1992, p21
28. Mintzes, op cit, p48
29. WHO, 1990, op cit, p14
30. Berer, op cit, p299
31. WHO, 1990, op cit, pp78-9
32. WHO, Special Programme of Research Development and Research Training in Human Reproduction, "Breast cancer, cervical cancer, and depot medroxyprogesterone acetate", *Lancet*, 24 Nov 1984, pp1207-8
33. WHO Collaborative Study of Neoplasia and Steroid Contraceptives, "Breast cancer and depot-medroxyprogesterone acetate: a multinational study", *Lancet*, Vol 338, 5 Oct 1991, pp833-8
34. Guillebaud, op cit, p198
35. Pardthaisong, T. and Gray, R.H., "In utero exposure to steroid contraceptives and outcome of pregnancy" and Gray, R.H. and Pardthaisong, T., "In utero exposure to steroid contraceptives and survival during infancy", *American Journal of Epidemiology*, Vol 134, No 8, 15 Oct 1991, pp795-803 and 804-11
36. WHO, 1990, op cit, p36
37. WHO, 1990, op cit, p17
38. Fraser, op cit, p119
39. Ibid, pp17, 66-7
40. WHO, 1990, op cit, pp55-7, 66-68 and 80-1
41. Population Information Program, "Long-Acting Progestins – Promise and Prospects", *Population Reports*, Series K, No 2, May 1983, pK-24

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Contraceptive freedom or coercion?

It took 24 years to develop, test and approve an implantable device, Norplant, that can prevent pregnancy for as long as five years. It took less than two weeks for Norplant to be billed as a new method of coercion. Within days of it being licensed in the USA, a Philadelphia newspaper published a racist editorial suggesting that Norplant might be of use in the fight against black poverty; a judge in California included the use of Norplant as part of the sentence against a woman found guilty of child abuse; and the state legislature in Kansas held hearings on a bill to encourage mothers receiving state welfare benefits to get the implant. Norplant's creator, Dr Sheldon Segal, commented at the time: "We created a method to enhance reproductive freedom and people keep finding ways to use it for the opposite purpose."[1] These practices were also condemned by the Board of Trustees of the American Medical Association.[2]

The first contraceptive implants, made of flexible, non-biodegradable tubes (Silastic) filled with hormones and placed under the skin, were developed in the 1960s. At least 10 hormones were tested in clinical trials, but the most promising was levonorgestrel. The US Population Council sponsored most of the research on implants and developed the system known as Norplant that is now manufactured by the Finnish company, Leiras. Norplant consists of six silicone rods, each filled with 36mg of levonorgestrel, which are inserted under the skin of a woman's upper arm. The hormone is then slowly and fairly consistently released into the body, retaining its contraceptive effect for five years. Its main mechanism of action is suppression of ovulation,[3] but it also makes the cervical mucus less penetrable by sperm and the lining of the uterus less able to accept a fertilised egg.[4]

Norplant was first registered in Finland in 1983, and has since been approved in a total of 26 countries worldwide. About 1.5 million women have used or currently use Norplant around the world.[5] The developers believe that this method is so safe and effective that it can be considered as "reversible sterilisation", and is likely to become very popular.[6] By the year 2000, there could be between four and seven million Norplant users in industrialised countries and 15 to 25 million users in developing countries.[7]

Efficacy

The overall (cumulative) pregnancy rate for the entire five years is only 2.7 to 3.9 per 100 users. This means that during the method's five-year period of effectiveness, around three to four out of every 100 users are likely to become pregnant.

Norplant's effectiveness is correlated with a woman's weight. Heavier women, particularly those who weigh more than 70 kilograms (approximately 154 pounds), have a higher probability of becoming pregnant after the second year of use than lighter women. The cumulative pregnancy rate after five years of use for women weighing over 70 kg is 8.5 per 100 women.[8]

Fertility apparently returns rapidly when the implant is removed. One study found that 50% of women conceived within three months and 86% within one year of removal of the implant.[9] The Population Council suggests that the figure might be as high as 88% within one year.[10]

Menstrual disturbances and other adverse effects

Implants, like other progestogen-only contraceptives, do disrupt the menstrual cycle. Irregular menstrual bleeding is the most common side effect, and the main reason for discontinuation.[11] A study of 234 Norplant users in the USA found that only 27% had regular menstrual cycles, 66% had irregular cycles and 7% had a complete absence of menstrual bleeding (amenorrhoea). By the fifth year of use, 62% of users had regular cycles, while 38% had irregular cycles, and there were no reports of amenorrhoea.[12] Overall, in clinical and field trials throughout the world, 60 to nearly 100% of Norplant users experienced irregular menstrual bleeding, usually at its most severe within the first six months after implantation.[13]

Other side effects include headache (reported by about 4 to 24% of women in different studies), dizziness, loss of appetite, weight changes (both gain and loss), nervousness, mood changes, breast tenderness, pain in the lower abdomen, pain and infection at the implant site, hair loss, acne and other skin problems.[14] Studies indicate that between 20 to 30% of pregnancies in Norplant users are ectopic.[15]

As the *Medical Letter* points out, "menstrual irregularities and other adverse effects may make the implants unacceptable to some patients".[16] Implants are not recommended for use in breastfeeding women, because the effects of the hormone on infants are not known.[17]

Like other hormonal methods, little is known about the possible long-term effects of implants. Equally, the effect of leaving the implant in place longer than five years is not fully known. The dose of progestin released gradually diminishes, leading to concerns that the risk of ectopic pregnancy or pregnancy with fetal exposure to progestin is higher.[17a] The fact that it happens is clear: 14 of 52 women followed up in Brazil were found to still have Norplant in place for longer

Proposed coercive Norplant legislation in the US: 1991 to early 1993

Proposals still pending in February 1993

Incentives for women on welfare (public assistance)[1]

Arizona and Washington: $500 + $50/year;
Colorado: $100;
Tennesseee: $500 for Norplant or vasectomy.

Reduced benefits without Norplant

Florida: welfare $258/month without Norplant, $400/month with Norplant, regardless of number of children;
South Carolina (2 bills): 1) no benefits to families with 2 or more children unless the mother has Norplant inserted, 2) no increase in payments with an additional child unless the mother uses Norplant;

Mandated Norplant use

Washington: involuntary insertion of Norplant with a court order for mothers of fetal alcohol syndrome or drug-addicted babies.

1991 and 1992 legislative poposals which have been rejected or withdrawn

Incentives for women on welfare

Kansas, Louisiana and Texas;

Reduced benefits without Norplant

Mississipi: welfare, food, housing and disability benefits cut if women with 4 or more children refuse Norplant;

Mandated Norplant use

Kansas and Colorado: condition for probation for women convicted of drug offences;
Ohio: drug rehabilitation or Norplant for mothers of drug-addicted babies;
South Carolina: court orders for Norplant authorised for mothers of babies testing positive for illegal drugs.

Note: Women on welfare receive contraceptives, including Norplant, free of charge in all states.
Sources: Alan Guttmacher Institute, *State Reproductive Health Monitor: Legislative Proposals and Actions*, Feb 1993, vol. 4(1) p6; Alan Guttmacher Institute, *Norplant: Opportunities and Perils For Low-Income Women*. Special Report #1, December 1992

than five years. Because the clinical trial they were taking part in had been stopped, the doctors who had inserted the Norplant had left the area and other doctors did not know how to remove the implants.[18]

Disadvantages

Certainly a serious disadvantage of Norplant is that women are dependent on health workers for removal of the implant. A study carried out in the Dominican Republic, Egypt, Indonesia and Thailand during 1986-7 found instances in all four countries where "removal on demand did not occur to the satisfaction of the user".[19]

Cost is another important disadvantage. The implant is one of the most expensive contraceptive options available – roughly double the cost of the pill and 18 times the cost of an IUD.[20] Even in the USA, a review of Norplant in the *Contraceptive Technology Update* commented that the price of the device, approximately US $300, plus insertion and removal costs, will prevent many low-income women from using it.[21]

The financial costs of Norplant for family planning programmes in developing countries may lead to a deterioration of other health services, as scarce resources are used to train health workers to provide the implants. The cost may also prevent the removal of the implants before the end of the five-year period. In Thailand, for example, "because of the cost of the method, women are routinely informed when choosing Norplant that the implants are appropriate for long-term spacing and will not be removed for minor side-effects."[22] Dr Sulaiman Sastrawinata, Executive Director of the Coordinating Board of Indonesian Fertility Research, says that Norplant "is an expensive method if it is not used for the [five-year] period it is meant to cover".[23] Health and family planning workers may be under some pressure to ensure that women do not stop using the implants prematurely.

Conditions for use

Norplant is a technology that requires a high standard of health care if it is to be administered safely. It is questionable whether such standards can be achieved in many developing countries, where most users are found. It is also questionable whether sufficient training and education can be provided for those who are inserting and removing the implants. The report of the four-country study in the Dominican Republic, Egypt, Indonesia and Thailand concluded that "service providers need further technical training in Norplant insertion, counselling, and removal."[24]

Information for women themselves is also far from ideal. In Bangladesh, for example, one of the first advertisements used to recruit women for the clinical trial of Norplant described it in glowing terms as "a wonderful innovation of modern science".[25]

The Population Council recognises the need for care in introducing Norplant because of its design. The Population Council says that it seeks settings for the introduction of Norplant where women can receive:

- a real choice of methods;
- accurate, balanced information;
- an easy relationship with the service provider;
- gentle, correct insertion;
- sensitive management of problems;
- access to removal on demand; and
- five-year removal.[26]

However, even where the Population Council has sponsored introductory trials or provided technical assistance to introduce Norplant in family planning programmes, these conditions are not always met.[27]

In Finland, one survey of physicians who had experience of inserting Norplant found that none of them considered the implant to be a first choice contraceptive. Similar findings are reflected in the literature about Norplant use in Finland: all the articles published in the 1980s suggest that Norplant should not replace existing methods in Finland and that the main market will be in developing countries.[28]

Policy makers from countries which have not yet introduced Norplant need to consider whether it provides an advantage over existing contraceptives. Can they meet acceptable guidelines for service delivery, including removal on request? Can they afford the cost of providing Norplant in the long run, including the cost of continued training in insertion and removal and the cost of follow-up of users to monitor their health and ensure that the implants are removed after five years?

Indonesia was the first country to use Norplant on a large scale, with more than 886,000 women having received the implant between 1987 and 1990. The implants proved highly successful when inserted by trained workers in a sterile environment in clinics, but problems arose when Norplant was included in the so-called "safari" programme – a programme where health workers visit a village for a day to recruit as many women as possible to use contraception. In such circumstances, individual counselling and information about side effects "tend to be minimal". A study by the Population Council found that many health workers received no formal training in insertion and removal techniques, leading to implants being placed deep in the muscle and their incomplete removal. The risk of infection was compounded by a lack of sterile equipment. Failure to identify already pregnant women also led to the implants having to be removed from a number of women. No abnormalities have yet been found in babies carried to term by these women, but

Norplant's effects on fetal development are not known, although progestogens generally are known to be potentially teratogenic. Despite a Population Council recommendation that the programme should proceed more slowly to allow time to train providers properly, the Indonesian government has started the programme in six more cities.[29]

It is not enough to say that certain conditions must be met and then turn a blind eye when they are not met; Norplant has a design which makes it prone to abuse because of the need for surgery for removal. Norplant was developed to have certain qualities: high effectiveness over a long period of time. These are useful qualities for family planning services which aim to reduce population growth quickly. However, this also means a lack of control by women and a high frequency of side effects that interfere with the quality of daily life.

Recommendations for action

1. If implants cannot be provided safely and respectfully and with a woman's fully informed choice, they should not be provided.
2. This means accepting that implants are not first choice contraceptives, removing them from the regular pharmaceutical market, and restricting their availability and use to those settings where conditions for safe use can be met. Their inclusion in most current family planning programmes will have to be reconsidered.
3. Any woman considering the use of an implant should have been fully informed about alternative methods and should have had the opportunity to try other methods for acceptability.
4. A woman who chooses an implant should first have been informed about the benefits and side effects of implants, and have been carefully examined for any possible contraindications. After receiving the implant she should be followed up for any adverse effects and have access to removal on request.
5. Research efforts should be focused on improving the availability and convenience of existing user-controlled methods of contraception including barrier methods.

References

1. Goodman, E., "Help to plan family size, not control the women", *International Herald Tribune*, 20 Feb 1991, p9
2. Board of Trustees, AMA, "Requirements or incentives by government for the use of long-acting contraceptives", *Journal of the American Medical Association*, Vol 267, No 13, 1 Apr 1992, pp1818-21
3. Segal, S.J., Alvarez-Sanchez, F., et al, "Norplant implants: the mechanism of contraceptive action", *Fertility and Sterility*, Vol 56, No 2, Aug 1991, pp273-7
4. Berer, M., "Contraception", chapter 15 in: Phillips, A., Rakusen, J. (eds) and the Boston Women's Health Collective, *The New Our Bodies, Ourselves* (2nd UK edition), London, Penguin Books, 1989, p300
5. Mintzes, B., Hardon, A. and Hanhart, J. (eds), *Norplant: Under her Skin*, Amsterdam, Women's Health Action Foundation and WEMOS, 1993, p2
6. Guillebaud, J., *Contraception: your questions answered*, London, Churchill Livingstone, (revised edn) 1991, p202
7. Stanley, B., "At arms length", *IDRC Reports*, Oct 1990, p19
8. WHO, *Norplant Contraceptive Subdermal Implants. Managerial and Technical Guidelines*, Geneva, World Health Organisation, 1990; Ollila, E., Kajesalo, K., and Hemminki, E., "Experience of Norplant by Finnish family planning practitioners", in: Mintzes, et al, op cit, pp47-68
9. Anon., "A subdermal progestin implant for long-term contraception", *The Medical Letter*, Vol 33, No 839, 8 Mar 1991, p17
10. Population Council, *Norplant: A summary of Scientific Data*, New York, Population Council, 1990
11. Anon., "Long-acting steroids provide new options", *Network*, Vol 9, No 3, Spring 1988, p7; Liskin, L., Blackburn, R. and Ghani, R. "Hormonal contraception: new long-acting methods" *Population Reports*, Series K, No 3, Baltimore, Population Information Program, 1987
12. Shoupe, D., Mishell, Jr., D.R., et al, "The significance of bleeding patterns in Norplant implant users", *Obstetrics and Gynecology*, Vol 77, No 2, Feb 1991, pp256-60
13. Townsend, S., "Norplant: safe and highly effective", *Network*, Vol 11, No 4, Dec 1990, p6
14. Berer, op cit, p300; Anon., *Medical Letter*, op cit, p18
15. Shoupe, et al, op cit
16. Anon., *Medical Letter*, op cit, p18
17. Berer, op cit, p300
17a Mintzes, et al, op cit, p2
18. Garcia, G. and Dacach, S., "Norplant – five years later [Brazil]", in: Mintzes, et al, op cit, pp69-79
19. Zimmerman, M., Haffey, J., et al, "Assessing the acceptability of Norplant implants in four countries: findings from focus group research", *Studies in Family Planning*, Vol 21, No 2, Mar/Apr 1990, p99
20. Stanley, op cit, p19
21. Anon., "Arrival of Norplant may be bittersweet for clinics," *Contraceptive Technology Update*, Vol 12, 1991, pp1-5
22. Zimmerman, et al, op cit, p99
23. Finger, W., "Programmatic challenges: training, counseling and removals", *Network*, Vol 11, No 4, Dec 1990, pp9-12
24. Zimmerman, et al, op cit, pp92-103
25. UBINIG, "The Norplant trial: an investigative study on the methodology and ethical issues", *The Hygeia*, Vol 3, Nos 1 and 2, 1988 (Jan-June), pp19-34
26. Beattie, K., "Introduction of new contraceptive methods: an opportunity for promoting the user's perspective in family planning programmes", in: Mintzes, B. (ed.), *A Question of Control: Women's Perspectives on the Development and Use of Contraceptive Technologies*, Amsterdam, WEMOS Women and Pharmaceuticals Project/HAI, 1992, p26
27. Zimmerman, et al, op cit, pp92-103
28. Ollila, et al, op cit, pp47-68
29. Anon., "Problems with Norplant in Indonesia", *Scrip*, No 1611, 26 Apr 1991, p26

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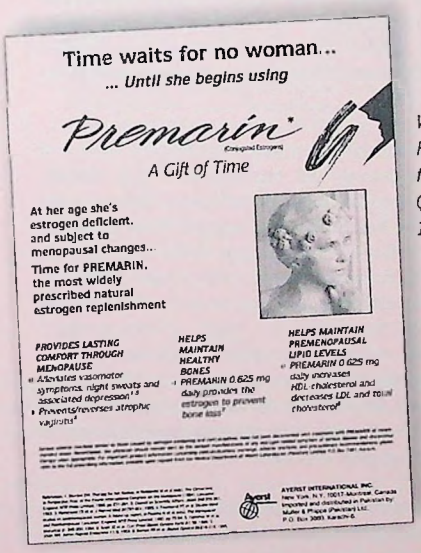
9A. Hormone replacement therapy

Selling eternal youth

Women are seen by the industry as "the market". At one symposium on menopause in Toronto sponsored by Ayerst, a representative from the industry commented to one of the organisers that the percentage of women taking Premarin [conjugated oestrogen] was notably lower than in the United States. He added, "There's a huge untapped market out there!"[1]

Take a population of healthy women in their late 40s or early 50s, women who are about to experience the end of menstruation (menopause), and convince them that they are running out of time, that their youth will be lost forever. Then tell them the good news: there's a way to hold back the hands of time – with oestrogen therapy. As one manufacturer, Wyeth/Ayerst, is fond of telling women all over the world: "Time waits for no woman... until she begins using... Premarin (conjugated estrogens)".[2] In Pakistan in 1990, women who used Premarin, were promised "a gift of time".[3] In 1990 in New Zealand, Schering advertised its oestrogen preparation in *New Zealand Doctor* with the headline: "So a woman can continue to enjoy being a woman".[4] In the United States, Ciba-Geigy told women that "the change of life" did not mean they had to change their participation in sports, or that men would no longer be interested in them. All they needed to do was use Ciba's Estraderm (transdermal oestrogen).[5]

Promoting oestrogens for postmenopausal women is a profitable business. The leading product in the field of "hormone replacement therapy" (HRT) is Wyeth-Ayerst's Premarin. It ranked 25th in terms of global sales in 1991, with total sales of $569 million.[6] In 1992, Premarin became the most widely prescribed drug in the USA. It also became Wyeth's best-selling product worldwide, with total sales of $642 million, accounting for over 17% of the company's pharmaceutical turnover.[7]



Wyeth/Ayerst ad for Premarin plays on fears of aging, QIMP, Pakistan, 1990

In the Philippines (PIMS, Dec 1988), Wyeth/Ayerst states that the indication for Premarin is "the estrogen deficiency state characteristic of the menopause and post-menopause"

Profitable it may be, but does it have anything to do with health? Is there any reason why 30% of post-menopausal women in the USA, and 10% of Australian and British women[8] should consume powerful hormones that are known to be associated with an increased risk of some forms of cancer? Yes, says the pharmaceutical industry, often with the support of vocal enthusiasts in the medical profession, and from some women themselves. No, not really, says the overwhelming body of scientific evidence.

Menopause is not an illness

Whether or not women have chosen to have children, the menopause marks a transition in a woman's life as the end of her reproductive years. How a woman experiences the menopause depends on the attitudes that she and society have towards aging in women, together with the extent and quality of her relationships with others.[9] "Menopause is not a disease, but a life-cycle transition," says medical anthropologist, Margaret Lock.[10] For most women, it is accomplished with minimal discomfort or need for medical intervention.[11]

Some women, however, may experience a variety of symptoms during the menopause – hot flushes, sweating, sleep and mood disturbances, dryness in the vagina. The hot flushes and vaginal dryness can be directly attributed to the change in the levels of hormones. So, hormone manufacturers have promoted the use of oestrogen as a way to deal with what has been called the "deficiency state" of menopause.[12] The whole concept of hormone replacement therapy is itself promotional. The hormones are not *missing*; they do not need to be replaced. Indeed, there are other options to treat these symptoms, as the box on the following page indicates.

However, efforts to convince women otherwise have a long history. During the 1960s, a New York gynaecologist, Dr Robert Wilson, is credited with mobilising opinion within medical circles and among women to use oestrogen to eliminate the unpleasant effects of the menopause. In 1963, with the aid of $1.3 million from the pharmaceutical industry, he set up the Wilson Foundation to promote oestrogen. Within 10 years, sales of oestrogen quadrupled in the USA. By 1975, oestrogen was one of the top five best selling drugs in the USA. The bubble burst when studies were published in the same year that linked oestrogen use to an increased risk of endometrial cancer.[13] Since that time, further studies have demonstrated without doubt that the long-term use of oestrogen only (unopposed oestrogen) leads to a three- to eight-fold increase in risk of endometrial cancer.[14] This has led to the practice of combining oestrogen with a progestogen – which is thought to counteract the effects of unopposed oestrogen.[15] However, there are still unresolved questions about what effect combined therapy might have.

In the Netherlands, Ciba Geigy calls Estraderm a "true-to-nature" substitute, Climacterium Journaal, March 1992

Osteoporosis

Osteoporosis – the loss of bone mass resulting in bones that are brittle and liable to fracture – is a significant and increasing problem in health care as populations grow older. Nonetheless, osteoporosis is rare in healthy premenopausal women with no history of fractures.[29] The decline in bone density is a natural aging process. There are two major types of osteoporosis: senile and postmenopausal. The causes of senile osteoporosis are related to the aging process and the condition is usually found in people over 70 years of age. It affects twice as many women as men. Postmenopausal osteoporosis is primarily linked to hormonal changes following menopause and the condition may be detected at any time from age 51 to 75. Although hormonal changes are important, they are not the only cause, as men can also suffer from this form of osteoporosis; however, the ratio of women to men is six to one. Ultimately, age-related bone loss accounts for more bone loss than can be attributed to the menopause.[30]

Dramatic statistics are often used to focus attention on the severity and cost of osteoporosis. It is an expensive disease because it can lead to a high number of hip and other fractures in elderly patients which often require hospitalisation and follow-up care. In 1992, the cost of treating osteoporotic hip fractures in the USA was estimated at some $7 billion.[31] There are 700,000 reported cases of hip fracture each year in Europe, Japan and the USA, and about 20% of patients die within six months from complications.[32] However, these deaths may be more connected with poor nutritional intake among the elderly rather than to the fracture or the osteoporosis.[33]

These hip fractures also may have little or nothing to do with postmenopausal osteoporosis. Hip fractures are more likely to occur after the age of 70 and result from age-related osteoporosis. HRT seems to be of little benefit. The most effective therapy is increased calcium intake.[34]

A study carried out in Australia found that bone loss can be slowed or prevented by exercise with either calcium supplementation or HRT. Although the exercise-HRT approach was more effective than exercise-calcium, it also caused more side effects, and therefore required medical supervision. As a result, the researchers concluded that if a common intervention was to be selected for all women, it would have to be increasing dietary calcium intake plus exercise.[35]

A question that is not always asked about medical treatments, but one which is becoming increasingly important in the light of economic constraints on health care systems in most countries, is how cost-effective they are.

Preliminary findings from one health region in the UK suggest that the use of HRT for 10 years from the time of menopause would lead to a reduction of hip fractures 20 years in the future of only some 5-10%, a reduction that would not result in any net cost savings.[36]

An analysis of HRT use in Australia found that although HRT for women with menopausal symptoms was generally cost-effective, for postmenopausal women who were not suffering from symptoms, prophylactic HRT for osteoporosis was not cost-effective.[37]

If HRT is given to prevent osteoporosis, it must be continued for at least 10 to 15 years. Stopped earlier, it seems to accelerate bone loss.[38] In other words, it does not *prevent*, but merely *postpones* the inevitable bone loss. Also, HRT only appears to be effective in postmenopausal osteoporosis. If fractures occur in postmenopausal osteoporosis, they are more likely to be spinal. Five to 30% of women who are receiving HRT at a dosage level considered to be sufficient to prevent bone loss nonetheless still suffer a reduction of bone density.[39] As well, most deaths in women with low bone mineral density are unrelated to the occurrence of fractures – "an observation that should be taken into account when estimating the need for and cost-effectiveness of bone-density screening and fracture prevention programmes".[40]

Non-drug therapy to prevent bone loss and fractures

Strategies for preventing osteoporosis work best when started early in life:

- Ensure sufficient dietary calcium in the teen years (this helps achieve optimal bone mass at maturity);
- Engage in exercises that place moderate stress on bones, such as walking, jogging and racquet sports;
- Stop smoking;
- Continue moderate exercise and avoid immobility after the age of menopause, to help keep bone density loss at a minimum;
- Minimise the risk of falling: in the home, avoid loose rugs, poor lighting, slippery surfaces; wear footwear that is supportive and provides a good grip; avoid unnecessary use of psychotropic drugs, many of which cause dizziness.

Sources: Urrows, S.T., Freston, M.S., and Pryor, D.L., "Profiles in osteoporosis", *American Journal of Nursing*, Dec 1991, pp33-9; Breslau, N.A., "Osteoporosis: Management", *Seminars in Nephrology*, Vol 12, No 2, Mar 1992, pp116-26; Forbes, A.P., "Fuller Albright: his concept of postmenopausal osteoporosis and what came of it", *Critical Orthopaedics and Related Research*, No 269, Aug 1991, pp128-141

Dr Fred Benjamin, associate director of obstetrics and gynaecology at Queens Hospital in New York, claims that "the *worldwide* consensus of doctors is that unless there is a contraindication, every menopausal woman should be given estrogen indefinitely to prevent osteoporosis and because of its other beneficial effects".[41] There is definitely *not* a global consensus. Dr Neil Breslau of the University of Texas South Western Medical Center, Center for Mineral Metabolism and Clinical Research, points out that "not every woman who becomes menopausal will develop osteoporosis."[42] Only about one woman in four is likely to develop severe and disabling osteoporosis in her later years.[43] According to Hans-Olav Adami, a leading Swedish researcher on HRT, "Randomised control trials are needed to provide the necessary basis for widespread preventive use of HRT."[44]

Clearing up misconceptions

Women who experience the menopause are not ill. Exposing them to a daily dose of hormones that are known to have the potential to cause life-threatening illness is not a decision to be taken lightly. So, why take HRT?

If the reason is to deal with the symptoms of menopause, then the number of women who need to use HRT is limited, and the duration of therapy should also be limited. In any event, there are effective non-drug alternatives which should be recommended first, as they are more cost-effective with less risk of adverse effects. If HRT is chosen, then by using the lowest possible dose to deal with the symptoms and by tapering off the dosage gradually, it should be possible to avoid a return of the symptoms once the HRT is stopped.

If the reason is prophylactic treatment of osteoporosis, then serious consideration needs to be given to the possibility that a woman may be on HRT for 30 years or more. There is no evidence yet to demonstrate what effects, either beneficial or adverse, such long-term therapy might have, although there are concerns about a possible increased risk of breast cancer with long-term therapy. There is also no solid evidence to show that the use of HRT will guarantee that a woman will not suffer from the ill effects of hip fractures later in life.

If the reason is prophylactic treatment of cardiovascular disease, there is not enough evidence to justify such therapy.

The clear message is that HRT is a therapy that has a limited usefulness. However, the pharmaceutical industry is pouring money into promoting HRT for as many women as possible.

In much of today's promotion, the three possible advantages – no menopausal symptoms, no fear of osteoporosis, and protection against heart disease – are often portrayed as being available in a trouble-free form. Although the widespread use of HRT is largely confined to industrialised countries and, within those countries, HRT is primarily used by women in higher socio-economic groups,[45] the pharmaceutical industry is also promoting HRT in developing countries.

What started as a sales campaign that "exploited existing socially-caused fears about aging and loss of status"[46] related to the menopause has now incorporated the fear of osteoporosis and the fear of heart attack as additional reasons to use HRT. Instead of more sales hype and emotive advertising, it is time for careful examination of the proper role of HRT.

Recommendations for action

1. HRT should *not* be recommended for widespread use by all menopausal or post-menopausal women.
2. Further research is required including controlled trials to study the overall benefits and risks of HRT.
3. Strict controls need to be introduced on the promotion of HRT.
4. Women considering using HRT to deal with the symptoms of menopause or for prevention of chronic disease should receive full, independent information about the risks and benefits, including non-drug options. For disease prevention, this should include an assessment of their personal risk and information on the effects of the specific type of therapy recommended on clinically meaningful endpoints such as hip fractures, heart attacks and stroke.

Risk of breast cancer

The possibility of an increased risk of breast cancer among users of oestrogen also caused sales to drop in many countries during the late 1970s and early 1980s. Breast cancer is the most common cancer in women in developed countries.[16] The use of oestrogen replacement therapy for 15 years is associated with a 30% increase in the risk of breast cancer, according to a meta-analysis of 16 studies.[17] An analysis of 10 studies of HRT use for more than eight years found a 25% increase in the risk of breast cancer.[18] A prospective study of more than 23,000 women in Sweden found that there was a 10% increase in the risk of breast cancer among those who took oestrogen replacement therapy. The risk increased with the duration of the therapy; women who used HRT for more than nine years had a 70% increase in the risk of breast cancer. The study also found that the addition of a progestogen "offered no protection against the development of breast cancer" although the number of women using combination HRT was small.[19] Another meta-analysis of 37 original studies found a 6% increase in the risk of breast cancer overall, but a 63% increase among long-term users (more than 12 years).[20] One major prospective study in the USA – the Nurses' Health Study – found no increased risk among past users, even those with more than 10 years of use; however, it found a 36% increase in risk among current users.[21]

There are problems with some of the studies. As with oral contraceptives, the dosage and type of HRT has changed over the years, making it difficult to evaluate the therapy being used today. Much of the research refers to high dosage forms of oestrogen-only therapy (unopposed oestrogens). Also, it is not always clear whether previous use of oral contraceptives has been taken into account in ascertaining risk.[22]

In addition to concerns about cancer, HRT is not without adverse effects, some of which are severe. These include headaches, breast tenderness, nausea, mood changes, dizziness, fibroids, and vitamin imbalances.[23] Oestrogen "may promote the development of certain classes of infections, particularly of the genitourinary tract",[24] and has also been linked to an increased risk of gallbladder disease.[25]

A lower risk of cardiovascular disease?

Two research findings in the mid-1980s brought HRT back into fashion. First, some studies found that women who used HRT were less likely to suffer heart attacks; and second, some studies found that the natural process of the decline in bone density was less severe among women who used HRT.

The risk of coronary heart disease among women who take oestrogens post-menopausally is 50% lower than among women who do not use HRT. There is also some indication of a similar reduction in the risk of stroke,[26] although a 10-year follow-up of more than 48,000 women in the Nurses' Health Study in the USA was not able to detect any change in the risk of stroke.[27]

However, there are problems with the use of HRT as a protective or preventive measure against heart disease. First, the evidence is based on the use of unopposed oestrogen only. Second, in most cases it is based on observational studies which may be biased by selection: because of their social and economic status, the women who were taking oestrogen might have been healthier and therefore at less risk anyway from heart disease. Not all the studies were able to control for this. Third, lifestyle changes are important preventive measures against heart disease that have not been adequately tested against drug therapy. In the absence of randomised clinical trials, the supporting data to recommend the widespread use of a drug for disease prevention is not available. Also lacking is the data to show what impact using oestrogen with a progestogen would have. Thus, the use of HRT to prevent cardiovascular disease is probably not a valid indication.[28]

Non-drug approaches for menopausal symptoms

- Stopping smoking;
- Decreased alcohol and caffeine intake;
- Weight-bearing exercise (walking, cycling, dancing, upper body workouts, aerobics, skipping, jogging);
- A diet rich in calcium and vitamin D, with plenty of vegetables and fruit;
- Relaxation techniques, meditation, or massage to reduce stress and depression;
- Maintaining regular sexual activity (for insomnia and/or vaginal dryness);
- Oil-based or water soluble lubricants for vaginal dryness;
- Wearing several layers of light clothing or carrying a folding fan to feel more comfortable in the event of hot flushes;
- Joining a support group.

Sources: in Phillips, A., Rakusen, J. (eds) and the Boston Women's Health Collective, *The New Our Bodies, Ourselves* (2nd UK edition), London: Penguin Books, 1989, pp454-9; National Women's Health Network, *Taking Hormones and Women's Health: Choices, Risks, Benefits*, Washington, 1989, pp6-7

References:

1. Ford, A.R., "Hormones: getting out of hand", in: McDonnell, K. (ed.), *Adverse Effects: Women and the Pharmaceutical Industry*, Penang, IOCU, 1986, pp27-40
2. Advertisement, *MIMS Caribbean*, January 1991, inside front cover
3. *QiMP*, Vol 22, Nos 1/2, Mar-Aug 1990, facing p70
4. Coney, S., "The exploitation of fear: hormone replacement therapy and the menopausal woman", in: Davis, P. (ed.), *For Health or Profit?: Medicine, the Pharmaceutical Industry, and the State in New Zealand*, Auckland, Oxford University Press, 1992, pp179-207
5. US Congress, Office of Technology Assessment, *The Menopause, Hormone Therapy, and Women's Health*, OTA-BP-BA-88, Washington, US Government Printing Office, May 1992, p71
6. Anon., "Top 25 products in 1991", *Scrip*, No 1717, 13 May 1992, p28
7. Anon., "New products boost AHP in 1992", *Scrip*, 1817, 4 May 1993, pp18-19
8. Coney, op cit
9. Roberts, P.I., "The menopause and hormone replacement therapy: views of women in general practice receiving hormone replacement therapy", *British Journal of General Practice*, Vol 41, Oct 1991, pp421-4
10. Lock, M., "Contested meanings of the menopause", *Lancet*, Vol 337, 25 May 1991, pp1270-2
11. National Women's Health Network, *Taking Hormones and Women's Health: Choices, Risks, Benefits*, Washington, 1989, pp2 and 6
12. Ford, op cit
13. Coney, op cit
14. Grady, D. and Ernster, V., "Invited commentary: Does postmenopausal therapy cause breast cancer?", *American Journal of Epidemiology*, Vol 134, No 12, 1991, pp1396-1400
15. Anon., "FDA committee recommends approval of oestrogen/progestogen use", *Scrip*, No 1632, 10 Jul 1991, p24
16. Sillero-Arenas, M., Delgado-Rodriguez, M., et al, "Menopausal hormone replacement therapy and breast cancer: a meta-analysis", *Obstetrics and Gynecology*, Vol 79, No 2, Feb 1992, pp286-94
17. Anon., "Breast cancer risk with long-term HRT", *Scrip*, No 1613, 3 May 1991, p25
18. Grady and Ernster, op cit
19. Bergkvist, L., Adami, H-O., et al, "The risk of breast cancer after estrogen and estrogen-progestin replacement", *New England Journal of Medicine*, Vol 321, No 5, 3 Aug 1989, pp293-7
20. Sillero-Arenas, et al, op cit
21. Colditz, G.A., Stampfer, M.J., et al, "Prospective study of estrogen replacement therapy and risk of breast cancer in postmenopausal women", *Journal of the American Medical Association*, Vol 264, No 20, 28 Nov 1990, pp2648-53
22. Goddard, M.K., "Hormone replacement therapy and breast cancer, endometrial cancer and cardiovascular disease: risks and benefits", *British Journal of General Practice*, Vol 42, Mar 1992, pp120-5
23. O'Donnell, M., "Improving on nature", *International Management*, Oct 1992, p87; Phillips, A., Rakusen, J. (eds) and the Boston Women's Health Collective, *The New Our Bodies, Ourselves* (2nd UK edition), London, Penguin Books, 1989, p457
24. Styrt, B. and Sugarman, B., "Estrogens and infection", *Reviews of Infectious Diseases*, Vol 13, 1991, pp1139-50
25. National Women's Health Network, op cit, p9
26. MacLennan, A., "Women, cardiovascular disease and hormone replacement therapy", *Medical Journal of Australia*, Vol 156, 20 Jan 1992, pp77-8
27. Stampfer, M.J., Colditz, G.A., et al, "Postmenopausal estrogen therapy and cardiovascular disease: ten-year follow-up from the Nurses' Health Study", *New England Journal of Medicine*, Vol 325, No 11, 12 Sep 1991, pp756-62
28. Barrett-Connor, E. and Bush, T.L., "Estrogen and coronary heart disease in women", *Journal of the American Medical Association*, Vol 265, No 14, 10 Apr 1991, pp1861-7
29. Urrows, S.T., Freston, M.S., and Pryor, D.L., "Profiles in osteoporosis", *American Journal of Nursing*, Dec 1991, pp33-39
30. Rubin, C.D., "Southwestern Internal Medicine Conference: Age-related osteoporosis", *American Journal of Medical Sciences*, Vol 301, No 4, Apr 1991, pp281-98
31. Gallagher, J.C., "Pathophysiology of osteoporosis", *Seminars in Nephrology*, Vol 12, No 2, Mar 1992, pp109-15
32. Anon., *The European Market for Osteoporosis Treatment Products*, London, Frost and Sullivan, 1992
33. Phillips and Rakusen, op cit, p469
34. Rubin, op cit
35. Prince, R.L., Smith, M., et al, "Prevention of postmenopausal osteoporosis: a comparative study of exercise, calcium supplementation, and hormone-replacement therapy", *New England Journal of Medicine*, Vol 325, No 17, 24 Oct 1991, pp1189-95
36. Pitt, F.A. and Brazier, J., "Hormone replacement therapy for osteoporosis", *Lancet*, Vol 335, 21 Apr 1990, p978
37. Cheung, A.P. and Wren, B.G., "A cost-effectiveness analysis of hormone replacement therapy in the menopause", *Medical Journal of Australia*, Vol 156, 2 Mar 1992, pp312-16
38. Urrows, et al, op cit; US Congress, op cit, p38
39. Stevenson, J.C., Cust, M.P, et al, "Effects of transdermal versus oral hormone replacement therapy on bone density in spinal and proximal femur in postmenopausal women", *Lancet*, Vol 336, 4 Aug 1990, pp265-9
40. Browner, W.S., Seeley, D.G., et al, "Non-trauma mortality in elderly women with low bone mineral density", *Lancet*, Vol 338, 10 Aug 1991, pp355-8
41. Eagan, A.B., "The estrogen fix", *Ms.*, Apr 1989, pp38-43
42. Breslau, N.A., "Osteoporosis: Management", *Seminars in Nephrology*, Vol 12, No 2, Mar 1992, pp116-26
43. Forbes, A.P., "Fuller Albright: his concept of postmenopausal osteoporosis and what came of it", *Critical Orthopaedics and Related Research*, No 269, Aug 1991, pp128-141
44. Adami, H-O., "Long-term consequences of estrogen and estrogen-progestin replacement", *Cancer Causes and Control*, Vol 3, 1992, pp83-90
45. Coney, op cit
46. Ibid

Problem Drugs was first published in 1986 and has been used by tens of thousands of health workers, pharmacists, policy makers, activists, researchers, students, journalists and others around the world. It has been translated into Arabic, Bangla, French, Indonesian and Spanish. This is an updated and revised version, with revisions based on a user survey.

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