

General Information

Rational and economic drug prescribing

Drugs often play a crucial role in the prevention and treatment of disease as well as in the alleviation of symptoms. While optimal or rational use of drugs is an obvious but imprecisely defined prerequisite for good medical practice, it has clear economic implications. Authorities in many countries are attempting to contain pharmaceutical expenditure both by limiting the number of reimbursable products and by disseminating information on alternative products, including their cost. Therapeutic choice is an issue that confronts practising doctors daily throughout their professional lives. Having decided that drug treatment is the appropriate therapeutic option, the doctor must give some thought to the financial implications of his decision.

The WHO Drug Utilization Research Group which last met in Cologne on 7-8 November 1985 has defined drug utilization as "the marketing, distribution, prescription and use of drugs in a society with special emphasis on the resulting medical, social and economic consequences".

The aim of the most recent meeting was to exchange information and views on the status and experience of drug utilization research projects and to design a strategy for future activities. Now that methods for data collection, presentation and analysis have been developed and refined it was considered that the Group should pursue a more action-oriented strategy. It was also appreciated, however, that the need remains to promote the study of drug utilization as a tool of value both to health authorities and to the health professions in general. Drug utilization data, it was recommended, should be included in national statistical records and they should be used to:

- describe patterns of drug use at various levels of the health care system;
- measure effects of educational, informational

and regulatory programmes, including price policies, and thus provide a basis for continuous adjustment;

- define areas for further investigation on the absolute and relative efficacy of drug therapy;
- aid in the determination of benefit/risk and cost/benefit ratios;
- indicate the over-use, under-use or misuse of individual drugs or therapeutic classes of drugs
- tentatively estimate drug needs in relation to morbidity patterns, thus aid in the planning of drug selection, supply, distribution and use as an element in national health planning.

Reference: Report of the WHO Drug Utilization Research Group, Cologne, 7-8 November 1985. World Health Organization Regional Office for Europe, Copenhagen, Denmark, 1986.

France - An official booklet entitled *Fiches de Transparence* has been issued to help prescribers select a pharmaceutical product within a given therapeutic class. It contains not only scientific information on the choice of products within a therapeutic category, but also economic information.

Within each therapeutic category, similar products are listed under brand and generic names. For each product information is provided on plasma half-life, price of a single dose and cost of daily treatment at recommended dosages.

Although the report does not cover the whole range of available drugs, it describes in twenty-one chapters the most important therapeutic classes.

The "Transparency Commission", which produced and updated this report since 1981, is primarily responsible for advising whether or not products should be placed on the *list of reimbursable products*. Products considered to offer either a therapeutic advantage or a saving in cost are listed for a

period of two and half years. At the end of this period, the Commission re-evaluates the product taking into account the extent to which the drug is prescribed and its performance in large scale use as opposed to the results of the premarketing clinical trials submitted at the time of first registration.

Reference: Fiches de Transparence (mise à jour Novembre 1985). Ministère des Affaires Sociales et de la Solidarité Nationale. Secrétariat d'Etat Chargé de la Santé. Direction de la Pharmacie et du Médicament. Paris, 1986.

The changing role of the pharmacist

United Kingdom - A Committee of enquiry was appointed in 1983 by the Nuffield Foundation with the following terms of reference:

"To consider the present and future structure of the practice of pharmacy in its several branches and its potential contribution to health care and to review the education and training of pharmacists accordingly".

The report, which was published in 1986, begins with a brief look at the profession, reviews the situation in each of its main branches—community, hospital and industrial—and turns to education and training, including undergraduate curricula, pre-registration training, continuing education, higher degrees and research. It ends with a list of 96 conclusions and recommendations. The views put forward by the Committee are summarized below.

Community pharmacy has developed in a way that now requires the pharmacist to be a shopkeeper. It is apparent that many pharmacies continue to be viable only because they form part of a shop selling other items unrelated to pharmaceuticals. Meanwhile the nature of dispensing has changed. The way in which medicines are now compounded has reduced the calls on the pharmacist's manipulative skills, while the rate at which potent new drugs are introduced has increased the potential demand on the pharmacist's knowledge. The extent to which the pharmacist will need to involve himself personally in dispensing will almost certainly continue to decline, but he will retain overall responsibility for the efficient, effective and safe conduct of the dispensing process; and his involvement will always be

needed in the minority of cases which call for the application of pharmaceutical knowledge at graduate level. Systematic arrangements are needed to enable pharmacists to cooperate with general practitioners to increase the effectiveness and reduce the costs of prescribing, and to help in the treatment of patients at home.

In *hospital pharmacy* the most significant development has been the introduction of "clinical pharmacy". This concept, however, seems to mean different things to different people. It has met with reserve in the medical profession on the grounds that clinical care is a matter for doctors, and that pharmacists should not seek to develop a clinical role for which they have no training or expertise. In fact, the clinical pharmacist in a hospital does not make decisions concerned with diagnosis. The doctor always determines the type of drug to be used, but the pharmacist can help in the selection of the most appropriate preparation. Although an experienced medical specialist can be expected to know more about the range of drugs used within his own specialty, the pharmacist has specialised knowledge that can contribute to the choice of drugs. He can help decide the best route of administration of a medicine; he is equipped to undertake the responsibility for selecting the formulation to be used; he may take specific responsibility for dosage calculations; and he should also be involved in the procedures for reporting suspected adverse drug reactions. In none of these respects is the pharmacist practising a clinical role that is or should be the responsibility of the doctor; on the contrary, the presence of a pharmacist permits the doctor to use the pharmacist's knowledge and experience to best advantage in the decisions on prescribing which are for him alone to take.

As far as *industrial pharmacy* is concerned, the pharmaceutical industry is not at present employing pharmacists on the scale which would serve its own interest and the national interest to best advantage. The "qualified person" having overall responsibility for the manufacture and control of medicinal products in each pharmaceutical company, as required by the relevant EEC directive, should be a pharmacist, rather than a chemist or a biochemist.

Reference: Pharmacy, A report of the Nuffield Foundation, Nuffield Lodge, Regent's Park, London NW1 4RS, United Kingdom, 1986.

Drug dispensing in hospitals

France -The Ministry of Social Affairs and National Solidarity has issued a document on *Good Practices for Dispensing Drugs in Hospitals* aimed at improving the quality and efficacy of health care and at keeping costs as low as possible. The document is intended particularly for pharmacists who are responsible for drug dispensing in hospitals and it outlines their responsibilities as follows:

- to analyse, from the pharmaceutical point of view, the physician's prescription,
- to provide information to assure the effective use of the prescribed drugs, and
- to prepare the dosage forms to be administered to the patient.

One section of the document deals with the need to devise a system of quality assurance for drug dispensing which requires the full collaboration of the prescribing physician, the dispensing pharmacist and the nurse administering the drugs to the patient.

Reference: *Pratiques de Bonne Dispensation des Médicaments en milieu hospitalier. Circulaire du 30 Janvier 1986 du Ministère des Affaires Sociales et de la Solidarité Nationale, Direction des Hôpitaux et Direction de la Pharmacie et du Médicament.*

Modern biotechnology

Biotechnology is a general term applied to any technique that utilizes living organisms (or parts of organisms) to make or modify products, to improve plants or animals, or to develop microorganisms for specific uses. A widely appreciated example of such technology is the process of fermentation which has been used from ancient times to produce wine, beer, bread and other fermented foods. Over the past decade attention has been focused on new techniques that constitute "modern biotechnology" or "genetic engineering".

Progress in biotechnology has already resulted in the production and marketing of medicines such as human insulin, human growth hormone, human serum albumin, interferons and some vaccines,

while monoclonal antibodies produced by cell fusion techniques are now used for diagnostic purposes. Other products still being developed are already under clinical investigation. Regulatory proteins, such as human growth factors, immune regulators and neurological peptides, which cannot be produced by traditional methods, may ultimately prove to be the largest areas of application of biotechnology in the pharmaceutical field.

Governments are reviewing existing drug legislation and regulations in order to adapt them to the new issues that are raised in the evaluation and control of biotechnology products.

Basic technologies

1. *Recombinant DNA (rDNA) technology* involves the joining of DNA fragments through the use of restriction enzymes. Gene fragments from a donor cell identified as serving a specific function are inserted into a vector (usually a plasmid). Using a process called "transformation" the vectors are introduced into a cell where they are able to reproduce. The transformed DNA material assumes the function of the new gene.

2. *Monoclonal antibody technology (cell fusion):* highly homogeneous monoclonal antibodies (MAB) are raised by injecting a mouse with a purified antigen. After a few weeks, the spleen of the mouse is removed and the induced B lymphocytes are fused with myeloma cells. The fused cells are either grown in culture or they are injected into the abdominal cavity of other mice (hybridoma). The resulting monoclonal antibodies produced by the hybridoma can then be collected and used. Antibodies produced by the traditional method of injecting an antigen into an animal and collecting the antiserum are heterogeneous, they can be produced only in small quantities and they are sometimes contaminated. The new technique allows production of large quantities of highly purified and homogeneous antibodies.

3. *Bioprocess technology:* fermented beverages and foods have been produced from the earliest times by this technology in which living cells or their components are used to effect a physical or chemical change. Modern biotechnology provides a potential for developing new organisms useful for bioprocessing.

National regulations and guidelines

Japan - Guidelines for rDNA research were initially developed only for research supported by public funds; however, private industry has since adopted them on a voluntary basis. The first *Guidelines for rDNA experiments involving plants or animals* were approved in 1984. A revised draft of *Guidelines for manufacture of drug products by application of recombinant DNA technologies* was issued by the Pharmaceutical Affairs Bureau of the Ministry of Health in June 1986. Comments are invited from the various parties concerned. It is expected that the final guidelines will be approved and published by the end of 1986.

United Kingdom - Guidelines on rDNA research have been developed by the Genetic Manipulation Advisory Group which apply to all relevant research in the United Kingdom. In 1984, the Group was replaced by the Advisory Committee on Genetic Manipulation in the Health and Safety Executive.

United States of America - The Office of Science and Technology Policy has issued a notice on "The Coordinated Framework for Regulation of Biotechnology". The document includes descriptions of the regulatory policies of the Food and Drug Administration, the Environmental Protection Agency and other federal agencies involved with the review of biotechnology research and products as well as interagency coordination mechanisms. As far as international aspects are concerned, the notice states:

"To facilitate data exchange and minimize trade barriers between countries, further developments such as testing methods, equipment design, and knowledge of microbial taxonomy should be considered at both national and international levels. Due account should be taken of ongoing work on standards within international organizations such as: World Health Organization, Commission of the European Communities, International Standards Organization, Food and Agricultural Organization; and, Microbial Strains Data Network."

Reference: *Federal Register*, Vol. 51, No. 123, 26 June 1986.

International guidelines

Commission of the European Communities -

In 1982, guidelines were issued which recommended that any laboratory conducting rDNA research should notify the competent national or regional authority in the Member State. Work is still progressing within the Committee for Proprietary Medicinal Products on the drafting of requirements for the production and quality control of medicinal products derived by recombinant DNA technology.

World Health Organization - A Laboratory

biosafety manual was prepared in 1983 containing guidelines for scientists in microbiological and biomedical laboratories. Only one page of the manual is devoted to rDNA research since the opinion of the experts consulted was that the attendant risks were no greater than those associated with known pathogens already covered in the manual.

Organization for Economic Cooperation and Development (OECD) - A report on

Recombinant DNA safety considerations was submitted to the Committee for Scientific and Technological Policy at its 43rd session on 5-6 February 1986. The report was drafted by the *ad hoc* Group on Safety and Regulations on Biotechnology within the following terms of reference:

1. to review country positions as to the safety in use of genetically engineered organisms at the industrial, agricultural and environmental levels against the background of existing or planned legislation and regulations for the handling of microorganisms, and
2. to identify what criteria have been or may be adopted for the monitoring or authorization for production and use of genetically engineered organisms in industry, agriculture and the environment, and to explore ways and means for monitoring future production and use of rDNA organisms.

New biotechnology products

United States of America - The Food and Drug Administration has approved marketing of :

- A vaccine for the prevention of hepatitis B, marketed under the name Recombivax HB® (Merck,

Sharp & Dohme). This is the first recombinant vaccine licensed by the FDA. It is produced by yeast cells into which the gene for production of the outer coat of the the hepatitis B virus has been inserted. Although the outer coat is not infective, it can provoke a protective reaction against the entire virus. The new vaccine should offer valuable protection to high-risk groups. Because the new vaccine can be given to newborns, infected pregnant women can be prevented from passing hepatitis B to the next generation. Three injections are recommended for individuals at high risk of contracting hepatitis B, including infants born to infected mothers. About 200,000 new hepatitis B infections occur each year in the United States and up to 10 percent of those infected become chronic carriers who are at risk of developing liver cirrhosis and liver cancer and who can infect family members and close contacts.

- Two *alpha interferon* products called Intron-A® produced by Schering Corp. and Roferon-A® produced by Hoffmann-La Roche Inc. The two companies developed their products independently; both are produced using recombinant DNA technology. The two preparations have been approved to treat hairy cell leukaemia. In studies involving more than 200 patients, alpha interferon produced partial or complete remissions of the disease in 75-90% of cases. While the mortality rate for the disease with conventional therapy is estimated at 7-20% a year, 92-94% of patients treated with interferon survived more than two years regardless of whether there was remission. Adverse reactions tend to be dose-related and include fatigue, fever, chills, nausea, and anorexia.

- A *monoclonal antibody that reverses acute kidney transplant rejections*, Orthoclone OKT3® (Ortho Pharmaceutical Corp.), produced using hybridoma technology. This binds to CD3-receptors on the surface of T-cells, which mediate the rejection of transplanted tissues. It is administered intravenously in bolus injections of 5 mg daily. In one clinical trial of the product, impending kidney rejections were reversed in about 94% of patients and, in another study, they were reversed in 65% of patients who had not responded well to conventional therapy. Adverse effects—most of which subside after the initial injections—include fever, chills, chest pain, tremors, dyspnea, and nausea.

Reference: *FDA Consumer*, Vol. 20, No. 7, Sept. 1986.

Epidemiology and drug safety

A new WHO/CIOMS initiative

The Council for International Organizations of Medical Sciences (CIOMS) is a nongovernmental scientific organization established in 1949 under the joint auspices of WHO and Unesco. CIOMS has offered for many years a free forum for discussions on policy matters between representatives of academia, national regulatory authorities and research-based pharmaceutical companies; when required, the Council convenes meetings of experts to make recommendations on specific issues. Over the past decade it has collaborated with WHO in a variety of matters, including guidelines on biomedical research involving human subjects, that relate to ethical aspects of medical research. In 1977, a Round Table Conference was convened by the Council on "Trends and Prospects in Drug Research and Development" (Reference: XIth CIOMS Round Table Conference, Bankowski Z & Dunne JF, ed. Scrip, Geneva 1978). The various collaborative projects that were subsequently realized have had immediate relevance to WHO's own commitment to therapeutic innovation. With the creation of its major research-based programmes in tropical diseases, diarrhoeal disease, and human reproduction, the Organization has focused much attention on the need for new approaches to the conquest of the major diseases endemic within the developing world. Its responsibilities are particularly onerous, since it both promotes and assesses innovative research. Already, several new synthetic drug substances and vaccines are under active investigation in man. Should one or more of these ultimately be accepted into routine use, their subsequent performance will need to be examined and assessed in countries where no system of spontaneous monitoring is in place. WHO thus shares with CIOMS a clear interest in developing a project concerned with reconciling the need for post-marketing surveillance with the epidemiological techniques and resources that are currently available.

Are drugs reasonably safe?

Having regard to the scale on which modern drugs are used throughout the world, there is little doubt that, within society as a whole, they are perceived

as necessary and beneficial, but, at the same time, the issue of drug safety is a matter of wide concern to the public and the media. Confidence in modern drugs is fragile and is at risk of further erosion unless public opinion can be satisfied that available resources for assuring the *reasonable safety* of marketed products are effectively deployed. As potent drugs cannot be absolutely safe, WHO and CIOMS aim:

- to present, objectively and persuasively, the benefits that society as a whole has derived from access to modern drugs and vaccines;
- to demonstrate that, if modern drugs are not misused, their benefits outweigh the risks of the diseases they cure or prevent and, for common ailments, that they present far less risk than those accepted in other aspects of daily life;
- to make the case that, unless society is prepared to accept remote risks to the individual as the corollary of effective medical care and therapeutic progress, it cannot demand progress in medical care and the development of better and safer drugs.

It is emphasized, however, that the last point can be propounded with conviction only if assurance can be provided that a responsible and committed effort is in hand to minimize drug-induced injury. Moreover, it can be projected with sincerity only by candid discussion of the strengths and weaknesses of preclinical toxicological studies as predictors of adverse effects in man, of the evident shortcomings of pre-marketing clinical studies as a basis of establishing safety—as opposed to the efficacy—of new drugs, and of the inability of spontaneous monitoring systems alone to assure the prompt detection of all unanticipated adverse effects of marketed products.

A balanced combination between toxicological evaluation and post-marketing surveillance

Whereas the deficiencies of the situation are manifest, perceptions of how to proceed have developed slowly. There has been reluctant acceptance on all sides of the reality that some aspects of a drug's performance can be definitively established only

from cumulative experience of its use in routine practice. Emphasis has consequently been slow to shift, in drug safety assessment, from a primarily experimental strategy based upon rigorous toxicological screening in animals, to a more balanced combination of toxicological evaluation and post-marketing surveillance. However, in recent years, pharmaceutical manufacturers have come to terms with the prospect that they face open-ended and searching reappraisals of the performance of their products throughout their commercial life-span. The impact of post-marketing surveillance on research-based companies is unquestionably evident from the recent and widely publicized withdrawals of several newly-introduced drugs on the basis of spontaneous reports of unanticipated toxicity. Wider application of epidemiologically-based studies could operate to intensify or even to allay this trend, but it will certainly not be without impact.

Epidemiological techniques

Unfortunately, post-marketing surveillance offers no simple solution to the problem of assuring drug safety. At least part of the problem seems to rest with doctors themselves since there is widespread acknowledgement—and some evidence—that they fail to report many serious suspected adverse drug effects to regulatory authorities. Epidemiologically-based studies, on the other hand, can be prohibitively expensive and experience has shown them to be vulnerable, even in the best hands, to random and systematic bias that can frustrate confident interpretation of the results. Who, then, should pay for such studies?

How should priorities be set? Is it feasible to create a coordinating apparatus to facilitate more effective deployment of available resources?

Moreover, some epidemiological techniques, notably case-control studies, offer a highly powerful statistical approach to the analysis of rare events and provide means of exploring absolute risks of 1:10,000 or less that in many other life situations would be accepted without demur: the challenge in these circumstances is not only to demonstrate the risk, but to evaluate what implications, if any, it should have for the continued availability of the product.

These questions may not lend themselves to resolution by consensus, but it is important that they be addressed in open debate not least because the capability of examining possible associations between drug exposure and subsequent adverse events, virtually at will, is about to arise in some countries from the application of record-linkage technique to existing data bases originally constructed for other purposes. What implications does this hold for pharmaceutical companies, for doctors, patients or society as a whole? What assurance can be provided about the quality of information held in such data bases? How can appropriate control groups best be constructed for purposes of comparison?

A cascade of similar questions presents itself to everyone responsible for, or involved in, drug safety assessment. For this reason, CIOMS has set out to provide a neutral forum for discussion of these issues at international level in the hope that some of them, at least, can be resolved to the benefit of society and to the satisfaction of regulators and the regulated alike.

Reference: *Monitoring and assessment of adverse drug effects*, CIOMS Working Group Report, Geneva, 1986.

Multistate licensing in the European Communities

The Commission of the European Communities has published a document providing general guidance on the use of the New Multi-State Procedure for Applying for Marketing Authorisation in accordance with the Council Directive 83/570/EEC.

Following the entry into force of this Directive in November 1985, the *minimum number of Member States to which a common application can be made has been reduced from five to two*. The purpose of the procedure is to facilitate the marketing in two or more Member States of a product which has been approved in any one of the Member States.

As the rules governing medicinal products have, to a large extent, been harmonized within the Member States, the authority(ies) of the Member State(s) to which the marketing authorization is submitted must

take into due consideration the authorization granted by the original Member State and have 120 days to put forward any reasoned objections to the *Committee for Proprietary Medicinal Products (CPMP)*. The Committee shall issue its own opinion on the grounds for the objections within 60 days and, within a further 60 days the authority(ies) must take a decision and inform the Committee accordingly.

The guide provides details of the documentation required for new drug applications, including documentation for abridged applications.

Reference: *NOTICE TO APPLICANTS for marketing authorizations for proprietary medicinal products in the Member States of the European Communities on the use of the new multistate procedure created by the Council Directive 83/570/EEC*. Luxembourg: Office for Official Publications of the European Communities. 1986.

Parenteral cephalosporins A review of indications

The Committee on Drugs and Pharmacotherapy of the Medical Association of Ontario (Canada) has outlined the main indications for parenteral cephalosporins.

First generation cephalosporins

- Treatment of some infections caused by *Staphylococcus epidermidis* and *Klebsiella pneumoniae*.
- As prophylaxis in operations involving the insertion of prosthetic material such as cardiac valves or prosthetic joints.
- As part of an antibiotic cocktail in the initial empirical treatment of the febrile neutropenic patient.

They are not effective in the treatment of meningitis because they do not cross the CNS barrier in adequate amounts.

Concurrent use of an aminoglycoside may act synergistically in producing nephrotoxicity, particularly when cefalotin is used with gentamicin.

Second generation cephalosporins are active against most of the bacterial pathogens causing pneumonia, but penicillin remains the drug of choice in the treatment of pneumococcal pneumonia. They

are used most commonly for peri-operative prophylaxis in colo-rectal and gynaecological surgery, in treating mixed infections caused by aerobic and anaerobic bacteria in these sites, in hospital-acquired aspiration pneumonia and in necrotizing soft tissue infection. Their shortcomings include a lack of activity against *Pseudomonas aeruginosa*, *Streptococcus faecalis*, and also frequently against *Bacteroides fragilis*, which may result in super-infection. Diarrhoea and pseudomembranous colitis may occur.

Third generation cephalosporins are active *in vitro* in very low concentrations against many Gram-negative aerobic bacilli. Their high potency and better penetration of the CNS make them effective in the treatment of meningitis caused by Gram-negative bacilli such as *Haemophilus influenzae*, *Escherichia coli* and *Klebsiella pneumoniae*. They are also effective against a wide range of Gram-negative bacilli, including many strains resistant to other antibiotics.

Reference: *The Drug Report*, published by the Ontario Medical Association, No. 18, January 1986.

Malaria vaccine trials

A Scientific Working Group of the UNDP/World Bank/WHO Special Programme on Research and Training in Tropical Diseases held a joint meeting in Geneva from 4 to 8 February 1985 to discuss the advances in the development of malaria vaccines.

At present, most of the relevant research is directed to *Plasmodium falciparum* and particularly to the sporozoites and the gametes that develop in the mosquito gut. The gene protecting the sporozoite antigen has already been cloned and the antigen produced in *Escherichia coli*. Three types of vaccines are expected to become available for field testing.

1. *Sporozoite vaccine* which, if fully effective, will prevent plasmodial development in the human host and thus induce parasite sterile immunity.

2. *Asexual erythrocytic-stage vaccine* which is expected to induce an immunity that will operate by

inhibiting the replication of asexual blood-stage parasites without inducing parasite sterile immunity.

3. *Transmission-blocking vaccine* which, if successful, will operate by inducing serum antibodies in the human host that block the fertilization of female gametes within the mosquito gut.

The vaccines that are ultimately developed are likely to consist of a protein of variable size produced by recombinant DNA technology or of small synthetic peptides coupled to a carrier. The general requirements for quality control of biologicals produced by recombinant DNA techniques have been published in the *WHO Bulletin* (61, 1983, pp. 897-911).

However, specific requirements have to be drawn up on a case-by-case basis. The Group noted that, before human trials can be contemplated, three conditions need to be met:

1. The need for the vaccine should be established and its feasibility realistically assessed.

2. The regulatory authority as well as the principal investigator should be satisfied that the preliminary laboratory and animal tests have provided the necessary information on the safety and efficacy of the candidate vaccine, and a clear indication of the potential benefits either to individuals or to communities or both.

3. Human trials should be conducted under the auspices or with the agreement of a nationally or internationally recognized ethical body; field trials of biologicals pose special problems that need to be considered in relation to contemporary ethical codes (*WHO Bulletin*, 55, Suppl. No 2, 1977, pp. 167-177).

The report provides details of the principles to be followed in malaria vaccine trials, including preclinical studies, clinical and field trials, and conditions under which studies might be conducted in order to evaluate the impact of immunization on transmission of the disease.

Reference: *Principles of malaria vaccine trials: report of a joint meeting of the Scientific Working Groups on Immunology of Malaria and on Applied Field Research in Malaria*. Document TDR/IMMAL-FIELDMAL/VAC/85.3., WHO, 1211 Geneva 27, Switzerland.

Airport malaria

Belgium - During the month of June 1986, five cases of malaria due to *Plasmodium falciparum* were reported among the customs officers working in the international airport of Brussels in a special terminal reserved for the transportation of goods.

Reference: *Weekly Epidemiological Record*, No. 30, p. 230, 25 July 1986.

Malaria chemoprophylaxis for travellers in endemic areas

As there is no drug which is entirely satisfactory for the prophylaxis of malaria, personal protection from mosquito contact is the most important preventive measure for travellers in endemic areas. Severe adverse reactions have been reported in travellers using the combination of chloroquine with sulfadoxine + pyrimethamine (Fansidar®) for prophylaxis.

Similar reactions associated with the prophylactic use of amodiaquine appear to be relatively high (approximately one in 2000); they include neutropenia and agranulocytosis; several deaths have been reported. It has consequently been recommended that amodiaquine should be used with great caution, if at all, for chemoprophylaxis of malaria.

Travellers to any endemic area should preferably use chloroquine in a weekly adult dosage of 300 mg base. Travellers to areas where chloroquine-resistant falciparum infections are prevalent, should carry a therapeutic dose (or, for longer exposure, several treatment doses) of sulfadoxine + pyrimethamine or mefloquine in case they should develop a severe febrile illness when access to prompt diagnosis and medical attention is not available.

Reference: *Weekly Epidemiological Record*, No. 15, p. 109, 11 April 1986.

Human insulin

When should it be used?

United Kingdom - Human insulin is produced by enzymatic modification of pork insulin or by genetic engineering; both techniques result in a product chemically identical with human endogenous insulin. The incidence of insulin antibodies in patients using human insulin (but not previously treated with animal insulins) has consistently been shown to be less than in those using beef or pork insulins. However, current evidence suggests the substitution of animal insulins with human insulin does not reduce antibody concentrations in patients that have previously used insulin, at least in the short term. As the costs of human insulin and purified pork insulins are now comparable, human insulin is considered to be the treatment of choice in patients embarking on insulin therapy. It should also be used in patients who require only short-term or intermittent treatment, such as gestational diabetics or type II diabetics undergoing surgery.

Reference: Northern Regional Health Authority, *Drug Newsletter*, No. 38, p. 154, June 1986. Newcastle upon Tyne, United Kingdom.

AIDS virus

Recommended name

The names "lymphadenopathy-associated virus" (LAV) and "human T-cell lymphotropic virus III" (HTLV-III) should be replaced by "*human immunodeficiency virus*" (HIV). This name will be used henceforth in all WHO publications and documents. In French the name recommended by WHO is "*virus de l'immunodéficience humaine*".

Reference: *Weekly Epidemiological Record*, No. 30, p. 229, 25 July 1986.

Drug therapy in AIDS and related symptoms

A recent review of the subject has been published by Sudhir Gupta in the October 1986 issue of *Trends in Pharmacological Sciences*.

Antiviral approaches

• **Zidovudine** (previously known as 3-azido-3-deoxythymidine, azidothymidine, AZT or BW-A 509U): this thymidine analogue is a potent inhibitor of both *in vitro* replication and the cytopathic effect of HIV. 19 patients had been treated with AZT for six weeks. Although immunological improvement was observed in some cases, it remains to be determined whether prolonged administration of the drug will be well tolerated, whether the improvement will be sustained and whether drug resistance will develop.

• **Suramin**: this drug, which is used in onchocerciasis and African trypanosomiasis, impairs *in vitro* infectivity and inhibits the cytopathic effect of HIV. At the University of California, 18 patients have been treated with suramin, but no clinical or immunological improvement was evident.

• **Antimoniotungstate (HPA-23)**: this compound is a competitive inhibitor of both murine and human retrovirus reverse transcriptases. Some patients treated in France showed transient resolution of HIV production and some improvement in the proportions of CD4+ cells, but after 15 days of treatment the virus could again be isolated.

Other antiviral agents that have been used in clinical trials include ribavirin, foscarnet sodium and AL-721.

Immunorestorative therapy

• **Thymic hormones**: thymosine fraction significantly improved the mixed lymphocyte culture reaction in a small-scale clinical trial. Thymopentin (TP5) has also been used in patients with AIDS-related syndromes and persistent generalized lymphadenopathy; some immunological improvement was observed, but further studies will be required to confirm the results.

• **Interleukin 2 (IL-2)**: this glycoprotein is necessary for normal differentiation, maturation and growth of T-cells. Immunological improvement, but no clinical improvement, has been observed in treated patients.

• **Interferons**: recent clinical trials with recombinant interferon alfa have shown some activity against Kaposi's sarcoma associated with AIDS.

Immunopharmacological agents

• **Isoprinosine** (inosine + dimepranol + acedoben): this anti-viral and immunopotentiating agent has been used in multicentre double-blind controlled placebo studies involving about 200 patients. Improvement in CD4 positive lymphocyte counts, natural killer cell activity, and conversion of delayed cutaneous hypersensitivity was reported in some patients, but none progressed clinically.

• **Ditiocarb sodium** (Imuthiol): this compound has been shown to inhibit *in vitro* infection with HIV of peripheral blood lymphocytes of the H9 cell line. Imuthiol was administered to 18 patients; eight patients showed immunological and clinical improvement, but long-term studies will be required to confirm the results.

Reference: *Trends in Pharmacological Sciences* 1986; 7: 393-397.

The impact of AIDS virus antibody testing

United States of America — The National Institutes of Health have sponsored a Consensus Development Conference on "The Impact of Routine HTLV-III Antibody Testing of Blood and Plasma Donors on Public Health".

Tests used to detect HIV infection:

1. Detection of the virus by culture.
2. Detection of antigens elaborated by the virus and present in the blood.
3. Detection of HIV-specific antibodies that are produced by the infected person's immune system using either the ELISA or the Western blot tests.

Current practice requires that all blood donors are ELISA tested. If the test result is negative, the unit of blood is acceptable. If there is a positive reaction, two further ELISA tests are performed on the same unit. In the nonprofit banking system the

Western blot test is used which is less likely to give false-positive or false-negative results. If the specimen is Western blot positive, the donor is regarded as infected with HIV. The most specific test for infectivity remains virus isolation; however, because of the complexity and difficulty of isolating HIV in cell culture, this is an impractical method for large-scale use.

Significance of positive tests results:

1. All persons who are antibody positive for HIV, whether they are symptom-free or ill, must be considered to be potentially infectious to others by sexual transmission, by sharing drug injection equipment, by childbearing, or by donation of blood, semen, or organs.

2. On current estimates, as many as 35% of HIV antibody-positive persons are likely to develop AIDS within a period of six to eight years.

3. All antibody-positive persons should seek information and advice on how to protect their sexual contacts and future children from infection.

The panel believed that there is a clear ethical responsibility on the part of the blood and plasma collection centres to notify individuals with repeatedly reactive blood in a sensitive, humane, and supportive manner. However, consideration should be given to the donor's cultural background and to the need to maintain confidentiality of the information.

Psychosocial consequences of a positive test result for blood donors :

Effects may be evident on the individual's psychological and physical health, subsequent sexual behaviour, and efficiency in work and other social roles.

Impact of testing on blood transfusion:

All possible steps should be taken to avoid unnecessary blood transfusion, especially in neonates, who may be particularly susceptible to HIV infection.

Impact on manufacturers of blood products and devices:

The plasma fractionation industry uses large pools of plasma for the preparation of certain clotting

factors concentrates. Despite highly sensitive tests, final production may contain infected units not detected by these assays. Reasonably successful methods have been developed to inactivate viruses in these products. Production of certain clotting factors by recombinant DNA techniques and monoclonal antibody methods will eventually eliminate such risks.

Reference: Office of Medical Applications of Research, National Institutes of Health, Bethesda, MD 20205, United States of America.

Safety of medicines

Current problems

United Kingdom - The Committee on Safety of Medicines reviews in "Current Problems":

- *Halothane hepatotoxicity:* an analysis of 251 reports indicated that 82% of patients had been exposed to halothane more than once, and 75% had been exposed at least twice within a period of 28 days. The risk of severe hepatotoxicity thus appears to be increased by repeated exposures within a short time interval, although susceptible patients remain at risk even when the interval between exposures is prolonged.

- *Neuroleptic malignant syndrome:* 17 cases (including 5 fatalities) of this uncommon, but life-threatening condition have been reported. The suspected drugs were haloperidol (4 cases), chlorpromazine (3 cases) and flupenthixol, clomipramine, dosulepin (one case each).

Reference: *Current problems*, No. 18, September 1986, Committee on Safety of Medicines, Market Towers, 1 Nine Elms Lane, London SW8 5NQ, United Kingdom.

Customized patient medication packages (Patient Med Pack)

United States of America - In the *United States Pharmacopoeia (USP XXI)* a new section has been added to the chapter on Containers. This

describes the Patient Med Pack, a package prepared by a pharmacist for a specific patient comprising a series of containers and containing two or more different solid oral dosage forms. The concept behind the Med Pack is to utilize the packaging to help the patient to take medications as instructed. The Med Pack is so designed—or each container is so labelled—as to indicate the day and time, or a period of time, during which the contents within each container are to be taken.

Reference: News of the United States Pharmacopeial Convention Inc., 12601 Twinbrook Parkway, Rockville, MD 20852, United States of America.

Smallpox eradication Nine years after the last case

The WHO Committee on Orthopoxvirus Infections now considers that the period of time that has elapsed since the occurrence of the last case of smallpox was notified is more than adequate to provide full assurance that naturally-occurring smallpox will not recur. The Committee considers that a reserve of smallpox vaccine is no longer required, but that stocks of seed virus for preparation of the vaccine should be retained by the WHO collaborating laboratories. Continuing investigation of monkeypox and related diseases should be encouraged.

Reference: *Weekly Epidemiological Record*, 61, No. 38, p.289, 19 September 1986.

Sexually transmitted diseases

United Kingdom - In 1984, nearly 621,000 cases were reported—a 4.2% increase over 1983. The data show a decline in both syphilis and gonorrhoea with virtually no change in the number of laboratory reports of β -lactamase-producing strains of gonococcus. In contrast, a rise in non-specific genital infections (previously non-gonococcal urethritis) is recorded, 50% of which were caused by *Chlamydia trachomatis*. Clinic returns showed a nearly 4-fold rise in herpes simplex infections, with

a larger increase in females. This gives rise to particular concern because of the association between infection with human papillomavirus, the causative agent of genital warts, and carcinoma of the cervix.

Reference: *Weekly Epidemiological Record*, 61, No. 43 p. 335, 24 October 1986.

Gonococci resistant to penicillin

Canada - The number of penicillinase-producing strains of *Neisseria gonorrhoeae* reported in Canada increased by 46% in 1984 as compared to the previous year. The minimum concentration of penicillin required to inhibit *in vitro* growth of 90% of gonococcal strains rose from 0.3 μ g/ml in 1973 to 2.0 μ g/ml in 1984. In many cases, strains with chromosomally-mediated penicillin resistance are genetically unstable and linked with resistance to other antimicrobial agents.

Reference: *Canada Diseases Weekly Report*, Vol. 11-21.

Gonococci resistant to tetracycline

United States of America - Between February 1985 and March 1986, 79 gonococcal strains showing high-level tetracycline resistance (defined as a minimal inhibitory concentration level of over 16 μ g/ml) were isolated and confirmed by the Centers for Disease Control (CDC), Atlanta. The high-level resistance to tetracycline is apparently a new characteristic developed by the gonococcus and is plasmid-mediated. Most of these strains were found to be sensitive to penicillin and to other antibiotics; only 3 of the 79 strains were also β -lactamase producing.

Reference: *Weekly Epidemiological Record*, 61, No. 36 p.277, 5 September 1986.

Injectable and implantable contraceptives

The WHO Special Programme of Research, Development and Research Training in Human Reproduction has issued two reports on contraceptives.

• **Injectable contraceptives:** two types of injectable contraceptives were studied, depot-medroxy-progesterone acetate (DMPA) and norethisterone enantate (NET-EN). These drugs appear to provide acceptable methods of fertility regulation. Clinical evidence derived from more than 15 years of use shows no additional, and possibly fewer adverse effects than are found with other hormonal methods of contraception.

• **Implantable contraceptives:** the report reviews clinical studies of Norplant and Silastic, subdermal implants that release levonorgestrel. The Capronor device, consisting of a single biodegradable capsule that delivers levonorgestrel for a period of 18 months, is still in clinical trial. Norplant, which is already established as an effective and reversible long-term method of fertility regulation, is considered suitable for use in family planning programmes, since it provides an important option for women desiring long-term contraception.

References: 1. *Facts about injectable contraceptives*.
2. *Facts about an implantable contraceptive*.
Both reports are available from the World Health Organization, 1211 Geneva 27, Switzerland.

1987 Vaccination Certificate Requirements and Health Advice for International Travellers

The new edition of this WHO publication is available in English and French from: *World Health Organization, Distribution and Sales, 1211 Geneva 27, Switzerland.*

Cough remedies

Italy - In the March 1986 issue of the *Drug Information Bulletin of the Ministry of Health*, L. Rossini reviews the mechanisms of action of currently available antitussive drugs.

Evidence of efficacy for many products, some of

which were introduced more than fifty years ago, is unsatisfactory and doubtful combination products are still widely used.

In 1974-1978, the consumption of antitussive products (mostly fixed combinations) in one region of Italy was 100,000 units per year for a population of 1.5 million. A similar survey conducted in 1984 confirmed this consumption pattern.

Reference: *Bollettino d'informazione sui Farmaci*, Ministero della Sanità, Direzione Generale del Servizio Farmaceutico, Rome, March 1986.

Drugs in the elderly

Singapore - The Department of Pharmacology of the Faculty of Medicine, National University of Singapore, issues at regular intervals a *Newsletter for Prescribers*. The January 1986 issue reviews adverse effects of drugs commonly used by elderly patients; precautions and contraindications are emphasized. Attention is drawn to the risks of various combination products containing a barbiturate currently available in Singapore and promoted for unwarranted indications.

Reference: *Newsletter*, Vol. 5, No. 1, January 1986, Department of Pharmacology, Faculty of Medicine, National University of Singapore, Kent Ridge, Singapore 0511.

Drug therapy of the depressed and hypertensive patient

Australia - Antihypertensive therapy in an already depressed patient must be selected carefully if aggravation of the depressive state is to be avoided. When depression arises in a patient receiving antihypertensive agents, a thorough evaluation of the possible reasons should be made.

The possibility of interactions between anti-depressant and antihypertensive medication should always be borne in mind, and a drug likely to produce the least disturbance in cardiovascular homeostasis should be chosen for treatment of depressed patients.

Particular care should be exercised in patients receiving lithium to prevent drug interactions and lithium toxicity.

Reference: *Australian Prescriber* 1986; 9: 42.

The "soft opiates" Marketing claims and objective evidence

Australia- The therapeutic action of available analgesic drugs is based on one of two mechanisms of action:

1. Antipyretic analgesics such as aspirin, paracetamol and other non-steroidal anti-inflammatory agents inhibit the synthesis of prostanoids (prostaglandins, prostacyclin, thromboxane A₂).
2. Opiates interact with endogenous opiate receptors in the central nervous system.

"Soft opiates", a somewhat cynical term, is applied to opiate analgesics such as codeine and dextro-propoxyphene (a methadone analogue) which are commonly administered in doses too low to have substantial analgesic effect. In adequate doses, these agents have the well known properties of all opiates—analgesia, but also adverse effects such as sedation, respiratory depression, constipation and typical dependence of the narcotic type. The place of "soft opiates" in therapeutics, it is contended, has been mainly determined by the influence of marketing and the desperation caused by intractable pain rather than by the weight of objective scientific evidence.

Reference: *Australian Prescriber* 1986; 9: 14.

Opiates for medical use

The International Narcotics Control Board has issued a special report on Demand and Supply of Opiates for Medical and Scientific Needs. The report provides an updated account of international efforts aimed at ensuring a proper balance between

legal demand and supply of opiates. It provides figures for world production and demand during the past 20 years and it describes the evolution of the cultivation of *Papaver somniferum* and of *Papaverum bracteatum* (a source of thebain).

Reference: *Demand and supply of opiates for medical and scientific needs*, International Narcotics Control Board, 1986, Vienna, Austria.

Action against illicit drug traffic

The United Nations Division of Narcotic Drugs organized a Meeting of Heads of National Drug Law Enforcement Agencies in Vienna from 28 July to 1 August 1986. The Meeting, which was attended by representatives of more than 80 countries, recommended that Governments take measures for the "tracing, freezing, seizing, forfeiture and confiscation of assets derived from illicit drug trafficking; improvement of extradition procedures; and development and use of active investigative techniques directed at organized crime". The meeting also adopted a series of other recommendations intended to strengthen law enforcement throughout the world.

Reference: *Information Letter* May-July 1986, Division of Narcotic Drugs, United Nations, P. O. Box 500, 1400-Vienna, Austria.

Basic tests for drugs in tropical countries

In tropical countries the degradation of drugs during storage and transportation is a serious problem. WHO has now published a manual under the title *Basic Tests for Pharmaceutical Substances*. These simplified or basic tests are not intended to replace the requirements of pharmacopoeial monographs, but they can be used in wholesale premises or pharmacies to verify the identity of pharmaceutical substances and sometimes to exclude gross degradation or adulteration. In several European countries such tests have already been endorsed by national pharmaceutical associations.

The methods used require a limited range of easily available reagents and equipment. They need not be carried out by fully qualified pharmacists or chemists, but they can be performed by persons such as pharmaceutical assistants. An expiry date determined for a temperate climate may be inappropriate in a tropical region even when adequate containers are used. For this reason, the stability characteristics of most of the substances referred to in the manual have been determined and tests to indicate gross degradation are presented for the least stable substances. Basic tests for finished pharmaceutical forms are planned to follow this publication.

Reference: *Basic Tests for Pharmaceutical Substances*, World Health Organization, 1211 Geneva 27, 1986.

WHO Chemical Reference Substances

An important aspect of WHO's role in international standardization in the pharmaceutical field is the provision of chemical reference substances by the WHO Collaborating Centre for Chemical Reference Substances in Stockholm, Sweden.

In his report for 1985, the Director of the Centre, Mr Bengt Öhrner, stated that 2210 packages of International Chemical Reference Substances and 22 sets of Melting Point Reference Substances were distributed to drug control laboratories in 46 countries. The fee for these substances has been kept unchanged at US\$ 25 per package. The report contains the list of substances available from the Centre. Orders should be sent to:

WHO Collaborating Centre for Chemical Reference Substances
Apoteksbolaget AB
Centrallaboratoriet
A-105 14 Stockholm, Sweden

Reference: Document WHO/PHARM/86.527.

Which formulation of nitrofurantoin?

United Kingdom - The differences between "conventional" tablets of nitrofurantoin (mean diameter of particles of 10 μm) and macrocrystalline tablets (diameter of particles of 75-180 μm) are discussed in the *Drug Newsletter* of the Northern Regional Health Authority.

The macrocrystalline formulation is claimed to dissolve more slowly within the gastrointestinal tract and to cause less nausea and vomiting. Although several of the clinical studies are judged to have serious weaknesses, the macrocrystalline formulation appears to have caused nausea and vomiting only half as often as conventional nitrofurantoin.

The macrocrystalline formulation is, however, substantially more expensive than the conventional formulations of generic and branded products.

Reference: *Drug Newsletter* of the Northern Health Authority, No. 39, August 1986, Newcastle Upon Tyne NE1 4LP, United Kingdom

Monitoring of adverse drug reactions The French system of pharmacovigilance

The system of monitoring unexpected or toxic drug reactions in France has been described by Professor R. J. Royer and others in the *Lancet*.

Since 1984 all prescribing physicians, midwives, or dentists have been required to report cases to their regional monitoring centre (Centre Régional de Pharmacovigilance); 29 such centres have been established to cover metropolitan France. They are located in university hospitals, either within a department of clinical pharmacology or a poisons treatment centre, and they are financed by the Ministry of Health.

The same method of reporting and assessing the possible relationship between adverse reactions and drugs is used by all regional centres. The reports are analysed and then entered into the national data bank (now totalling over 26,000 cases). All centre directors meet in Paris every other month at the Ministry of Health to report unusual events, to compare cases and to suggest regulatory measures. A great advantage of the system is that each regional centre has close contact with the local doctors.

Reference: *Lancet* 1985, 2: 1056-1058.

Western cholelithiasis and Asiatic primary cholangitis

Singapore - In the *Drug Information Newsletter* of the Department of Pharmacology of the National University of Singapore, Prof. T. K. Ti reviews the clinical and therapeutic aspects of gallstone disease in Singapore where it is important to make a distinction between two disease entities.

Like the Western disease, the Asiatic disease—known variously as primary cholangitis, oriental cholangitis or cholangiohepatitis—occurs usually in middle and old age but, unlike the Western disease, it does not occur predominantly in women.

The typical presentation of the two diseases differ—the Western disease typically presenting with right hypochondrial pain, with or without fever, and the Asiatic disease with high fever, chills and jaundice as a result of empyema or cholangitis. In other cases, however, the Asiatic disease remains dormant for years and may present with dyspepsia, or biliary colic, without jaundice or fever.

While cholecystectomy, sometimes together with exploration of the bile duct, cures the Western disease, biliary intestinal drainage is usually required for Asiatic cholangitis. Even so, 25% of these patients subsequently develop recurrent symptoms and require further treatment.

Drug therapy, it is considered, has yet to make a major impact in the management of gallstone disease.

Reference: *Drug Information Newsletter*, Vol. 5, No. 4, October 1986, Department of Pharmacology, National University of Singapore.

Limulus amoebocyte lysate (LAL) test for bacterial endotoxin

The *European Pharmacopoeia* has now adopted the limulus test for bacterial endotoxin (document PAPH/Exp. 1L/T [86]4). The test is not intended, however, to replace completely the rabbit pyrogen test: each test has its own merits and field of application.

The test uses a lysate of amoebocytes from the horseshoe crab, *Limulus polyphemus*.

The addition of a solution containing endotoxins to a solution of the lysate produces turbidity, precipitation and gelation.

Reference: *Medicines Act Information Letter* issued by the Department of Health and Social Security, October 1986, London, United Kingdom.

Animals in medical experimentation

United Kingdom - In *Frame News*, published by the Fund for the Replacement of Animals in Medical Experiments, two solutions are described to the animal experimentation problem—revolutionary and evolutionary.

The former solution has been sought for more than 100 years by generations of antivivisectionists, who have campaigned with sincerity on moral grounds for a total ban on all experiments on living animals.

Frame, however, was founded to support the evolutionary approach, and therefore unhesitatingly applauds the passage of the Animals (Scientific Procedures) Act 1986, which offers great possibilities for reform in line with three basic principles, namely reduction, refinement and replacement.

Disaster would result if scientists seeking acclaim, politicians needing votes, and industries seeking an improved public image permitted the introduction of alternative tests which were later found to be unreliable—but only *after* the assurance they had helped to provide had allowed hazardous new products to be put on the market.

Alternative *in vitro* tests can be accepted if they have passed through the following stages of development:

- *Initial phase*: basic procedure is defined and decisions are made regarding culture method, cell type, culture medium, end-point to be measured as a means of assessing cell damage, and the method to be used for its measurement; a study carried out with a small group of model chemicals and reproducibility within the laboratory is assessed; a definitive test protocol is worked out.
- *Consolidation phase*: all previous decisions are challenged. The same set of model chemicals is used to see whether different results would be obtained if other cells, media, end-points or assay methods were used.
- *Validation*: this is primarily a question of scientific quality control involving an assessment of the test's ability to predict toxicity of a large number of chemicals, a blind trial with at least 50 chemicals, and independent assessment of the results.
- *Evaluation*: assessment of the applicability of the test to real problems, and consideration of feasibility and necessity in relation to conventional animal tests.

Frame has collected 100 chemicals, from which appropriate sets can be selected for the blind validation of developed *in vitro* tests for general cytotoxicity, irritancy, metabolism-mediated toxicity, neurotoxicity, and embryotoxicity.

The main difficulty in alternative research is the nature, source and quality of *in vivo* data to be used in *in vitro/in vivo* comparisons. The published data, particularly on acute and long-term toxicity, carcinogenicity, and reproductive toxicity in the whole animal are not of an even or high quality. Nor is it clear which criteria for *in vivo* toxicity should be used. LD50 values and Draize Test scores are tempting indicators, but the one is plagued by interspecies differences and interlaboratory variation, while the other is based on subjective assessments and is, at best, only semi-quantitative.

Reference: *Frame News*, No. 12, September 1986, Eastgate House, 34 Stoney Street, Nottingham NG1 1NB, United Kingdom.

The pharmaceutical market in Nigeria

Nigeria - Nigeria's pharmaceutical market, like the rest of the economy, has contracted substantially since 1979. The total drug market, estimated in factory prices at US\$ 204 million in 1979, grew to US\$ 292 million in 1983, with a decline in average growth from about 15% in the 1976-1979 period to about 9.4% in the 1979-1983 period.

Nigeria was the biggest pharmaceutical market in Africa, but by 1983 it was third largest after Egypt and Algeria.

Leading Pharmaceutical Markets in Africa in 1983
(in US\$ millions at ex factory prices)

	Value	Share
1. Egypt	490.00	27.73
2. Algeria	300.00	16.98
3. Nigeria	292.00	16.52
4. Morocco	114.50	6.48
5. Libya	79.50	4.50
6. Tunisia	60.50	3.42
7. Sudan	55.50	3.14
8. Kenya	53.00	3.00
9. Côte d'Ivoire	49.25	2.79
10. Cameroon	38.00	2.15

The contribution of local production to the total pharmaceutical market grew in Nigeria from about 5% of the market in 1976 to 25% in 1983, but it has remained stagnant since then. Local profit margins are below 25% for most drugs, and the bulk of local products are simple OTC analgesics and vitamins.

The Second-tier Foreign Exchange Market (SFEM) operates on the principle of a money market where buyers and sellers purchase and sell foreign currencies from and to the government-authorized dealers. SFEM is a national economic strategy introduced recently and designed to:

1. Efficiently ration scarce foreign exchange among competing national users.
2. Gradually reduce the degree of over-evaluation of the national currency (the naira).

3. Discourage import dependence.

4. Strengthen competitiveness of Nigeria's non-oil products in international markets.

It is expected that SFEM will increase exports of drugs, but the high foreign content of local products will negate competitiveness in foreign markets. Innovative pharmacists will begin to derive worthwhile returns for such activities as improvised product packaging, presentation, new inventions and formulations. Traditional medicines, because of their high local content and cost advantage, will find favour, but vigilance will be required to stem fraudulent practices.

Reference: *Pharmaceutical World*, Vol. 3, No. 5, September/October 1986, Ikeja, Lagos, Nigeria.