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THERAPEUTIC NEEDS AND PRODUCTION OF DRUGS 1/

presented by the

World Health Organization

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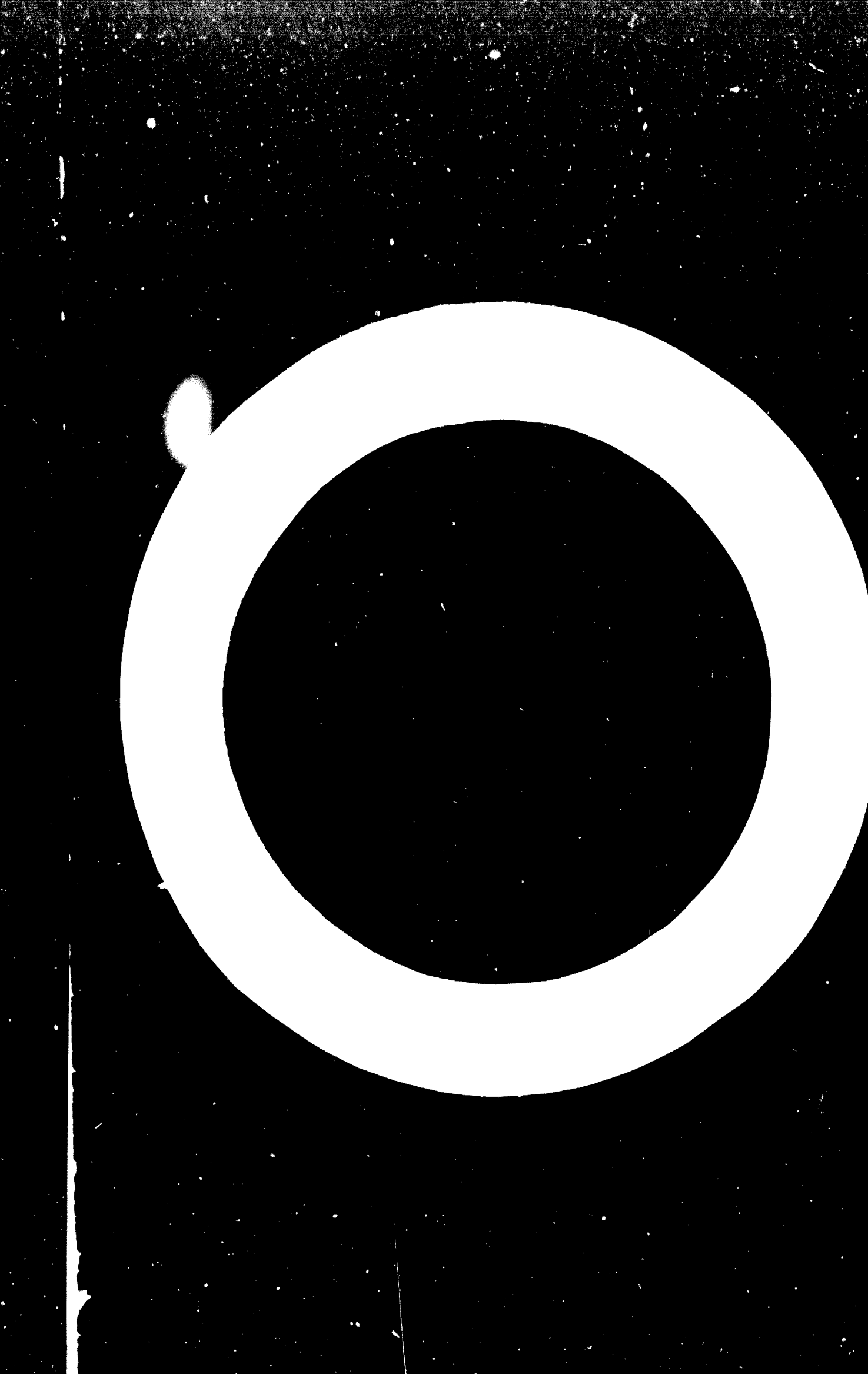


The pattern of drug treatment varies from country to country and depends on a multiplicity of modifying factors. Three of them which influence drug therapy under the particular conditions of developing countries are discussed in some detail: cost; simplicity of administration, and stability under special climatic conditions. These factors have to be taken into account in the planning of local pharmaceutical production, but the assessment of the actual therapeutic needs should be the fundamental consideration in establishing a pharmaceutical industry destined to supply predominantly the home market.

Further, the paper deals with the professional qualifications of advisers on therapeutics as well as the sources of information on drug prescribing and consumption habits, which are required for the initial as well as continuous information of the pharmaceutical industry.

The reasons are explained for the continuing progress in drug research which of necessity causes a continuous change in production programmes. Hence, permanent co-operation between industry and medical advisers is imperative.

There are a number of services, which can be provided in this connection, by the medical units of the Division of Pharmacology and Toxicology of the headquarters of WHO.

1.1 CONSUMPTION OF DRUGS AND ENVIRONMENTAL FACTORS

The administration of medical care varies in different areas all over the world. Uniformity cannot be expected or achieved because the organization, the facilities, the subjects and the extent of medical care, offered to the individual and the community, are greatly influenced and modified by the environment. Modifying factors are, for example, the prevalence of infectious and other diseases, the existence of genetic disorders, the health security systems, the availability of physicians, pharmacists, nurses, laboratories and hospitals, and last, but not least, of pharmaceutical products.

Even if we select a circumscribed item of medical activity e.g. the treatment of patients with drugs, we find that the way in which drug treatment is practised in different countries differs greatly according to environmental conditions. In a country where the doctor/patient ratio is 1 to 100,000, as in certain African regions, drug prescription and consumption habits will be totally different from those of countries where the ratio is 1 to 1,000, or even less as in some European countries. Therapeutic practice, however, determines, together with some other factors, the consumption of pharmaceutical products.

1.2 Examples for Special Therapeutic Conditions in Developing Countries

I would like to illustrate this by examples chosen from the drug therapy of tuberculosis.

1.2.1 The Role of Treatment Costs

Firstly, I refer to the importance of treatment costs for the choice of drugs and therefore for the consumption and production of drugs: under North American or European living conditions, the choice of drugs to be used in the treatment of tuberculosis would be predominently dependent on

their antibiotic and toxic properties and on the prevalence of drug resistant strains in the area. Under the aspects of expected benefit and risk the antituberculous drugs of first choice in those countries are isoniazid, paraaminosalicylic acid and streptomycin. Viomycin, cycloserine and kanamycin should be used under exceptional conditions only. They cause more severe and more frequent adverse reactions. They are administered in case of drug-resistance, as observed in 10 to 60 per cent of the drug treated patients (Özer, O., Erelçin, H.; Prax. Pneumol. 22, 224 (1968)). The order of criteria to be used for the selection of the drug of choice under normal living conditions would be: first the incidence of adverse reactions, second the frequency of primary or acquired drug-resistance, third the treatment costs.

Let us direct our attention to the treatment conditions in certain developing countries of low economic potential, in countries where neither the patient can pay for his treatment nor are the government's funds sufficient to provide adequate care for everyone who requires drug treatment. Under such circumstances, the minimal amount of money which must be spent for a single patient, in order to perform effective treatment, becomes the critical figure which determines the choice of drug, because the drug which provides the cheapest treatment per person allows the treatment of the greatest number of sick. Under those conditions treatment costs will be the primary factor, while toxicity and resistance might well be of secondary importance.

The following table shows four drugs used effectively in the treatment of tuberculosis; isoniazid, thiacetazone, paraaminosalicylic acid and streptomycin. The table includes standard daily dosage and the annual cost of treatment per patient in dollars, as calculated from hospital records in Uganda several years ago.

Drug	Standard Adult Daily Dose	Cost per year in $
Isoniazid	300 mg	0.90
Thiacetazone	150 mg	1.00
Paraaminosalicylic acid	10 g	9.25
Streptomycin	1 g	17.25

It is quite obvious from the figures that because of their low price isoniazid and thiacetazone would be the drugs of choice in such a poor country and that the predominant prescription of those drugs would be advisable. The factor of acquired resistance under such conditions would have to be neglected, since its identification in the individual case, as a rule, would be technically and organizationally impossible.

In other areas, where the economic situation is less serious and the health service better developed and financed, the therapeutic needs may be covered satisfactorily only if a broader spectrum of antituberculous drugs will be available, enabling physicians to choose more freely between alternative drugs, in accordance with the needs of the individual case.

1.2.2 Simplicity of drug administration

The factor, simplicity of drug administration, which I also mentioned, has little influence on consumption of drugs, so long as a sufficient number of physicians, nurses and hospital beds are available for those patients who need, for example, long-term treatment by a drug which cannot be injected or the application of which must be controlled by a continuous analysis of body fluids. Consequently, the form in which a drug has to be administered therapeutically would have little influence on the choice of drugs, if enough hospital beds are available (which is a rare exception).

But where the daily treatment of patients cannot be provided this way, and where patients receive at best hospital care intermittently, and have to return to their homes at some distance, drugs that have to be injected cannot be administered. Under those conditions drugs, which

can be given orally, will be the drugs of choice even if they are not as satisfactory as injectable drugs. The treatment of tuberculous patients with streptomycin, for example would be impossible under these conditions.

1.2.3 Tropical Climate and Drug Stability

If then you would allow me to illustrate the influence of a tropical climate, with high humidity and high temperature, on the choice of antituberculous drugs, I would refer to the instability of cycloserine, which deteriorates quickly under such conditions. [K.V. Nageswara Rao and others, Bull. Wld. Hlth. Org. 25, 701 (1958)] Cycloserine, therefore, would have to be excluded from the list of recommended drugs if the necessary provisions for the maintenance of its antibiotic activity could not be established.

It is evident that the aforementioned factors determine the actual therapeutic needs within a given area as well as local drug consumption and production as such.

1.3 Local Therapeutic Needs and Drug Production

Whether production lines of pharmaceutical industries do reflect the prevailing prescription trends active in the respective areas remains to be studied. Such an investigation may be feasible so far as prescription drugs are concerned. It would be difficult as regards over the counter products, though such products merit attention under the aspects of public health, national economy and technical assistance. Also, a pharmaceutical industry established on the basis of a partnership between an international organization and a governmental agency would in any case have to respect the true therapeutic needs of this country, and its programme should contribute to the national public health service.

The exploration of therapeutic needs should be initiated in advance of the establishment of a pharmaceutical project. It will require a continuous degree of co-operation between local pharmaceutical and medical specialists and the pharmaceutical industry. Such a recommendation may seem a triviality. However, there are examples of shortcomings in this field. A prominent official of the Ministry for Economical Co-operation in Bonn stated recently, after an inspection of several bilateral projects in Africa, that such projects are often hampered because local specialists had not been consulted in the planning or revision of projects, and that this is often the case with projects in the health field which have not been planned economically (Hea. Tribune 7.2.69).

It would be a mistake to expect that the establishment and running of a pharmaceutical factory in a developing country would imply less planning effort than would be necessary in an industrial area. In fact, the establishment of pharmaceutical industries in areas of rapid development is in some respect more complex than under conditions of so-called normal economic development. For example, pharmaceutical industries, operating in highly industrialized areas, usually consider first of all the efficacy and safety of the drugs developed or produced by them and secondly the actual market conditions. The production lines of pharmaceutical industries, operating in less developed areas are, in addition, determined by factors which would not be as prominent in other areas, for example, the availability of raw material and power, of equipment, of trained scientists and craftsmanship.

2. EXPLORATION OF THERAPEUTIC NEEDS

How can local therapeutic needs be explored, analysed and evaluated ? No doubt other speakers will make a more detailed investigation of this matter. Nevertheless, I would like to stress the need for the planning group to co-operate with local pharmaceutical and medical specialists, who are able to assist in, or to perform, the collection, analysis, and evaluation of available information on therapeutic needs.

2.1 Professional Qualities of Consultants

Firstly, what sort of specialists are needed to obtain pertinent information" Specialists, experienced in international drug trade, may be inclined to analyse first of all figures related to the importation of drugs. Those who are specialized in the analysis of local drug trade figures may base their advice mainly on sales figures obtained from public pharmacies. These figures will provide valuable information, but to not necessarily reflect the actual therapeutic needs of an area. Information which uncovers the true therapeutic needs may be obtained from physicians, preferably pharmacologists; from statistical data on drug consumption provided by Sickness Insurance Boards; from records of hospital and military pharmacies; and from the prescriptions of representative samples of hospital doctors and practitioners in urban and rural areas.

A pilot study of that kind was undertaken in 1966 and 1967 in some European countries on behalf of the Regional Office for Europe of WHO. For future work in this field the methods used in this study will have to be refined and then may be of considerable value also for the analysis of therapeutic needs in developing countries.

2.2 Selection of essential drugs

Once figures are available of products necessary for sound medical care a realistic selection of the items, which can be produced locally, will become possible. In the next table two sections are shown of a list of a total of 140 drugs, which were considered to be essential and sufficient, i.e., adequate for the purposes of everyday therapy in a hospital in Uganda, though some of the drugs are required for occasional use only. This example was published for a symposium on medical care in developing countries at Makerere in Uganda in 1966 (M. King; Medical Care in Developing Countries, Nairobi, Oxford Univ. Press, 1966).

LIST OF DRUGS

(by M. King, Kampala, Uganda)

(containing a fraction only of the total of 140 items)

Drugs acting on the cardiovascular system

Aminophylline, inj. amps.

Adrenaline tartarate, inj. amps.

Nor-Adrenaline, inj. 4 mg. amps.

Methyl amphetamine ('Methedrine') inj. 30 mg. amps.

Prepared digitalis. 65 mg. tabs.

Digoxin, 0.25 mg. tabs.

Digoxin, inj. 0.5 mg. amps.

Heparin, inj. 1,000 units per ml. vials.

Protamine sulphate inj. 1% vials (Heparin antidote)

Drugs acting on the nervous system

Acetylsalicylic acid, 300 mg. tabs.

Ergotamine, 1 mg. tabs.

Morphine sulphate, inj. amps. 15 mg.

Phenobarbitone, 30 mg. tabs.

Pethidine 50 mg. tabs.

Pethidine hydrochloride, inj. 50 mg. amps.

Amylobarbitone sodium ('Amytal'), 65 mg. caps.

Phenobarbitone 30 mg. tabs.

Sodium phenobarbitone, inj. 200 mg. amps.

Paraldehyde, inj. 10 ml. amps.

Epanutin, 100 mg. caps.

Chlorpromazine ('Largactil') 25 mg. tabs.

Chlorpromazine, inj. 50 mg. amps.

Chloral hydrate crystals.

Lignocaine without adrenaline, 2% vials

2.3 Revision of lists of selected drugs

An expert in clinical pharmacology, after a critical analysis of the list, may conclude that some of the drugs are outdated and others are scarcely effective when judged by modern criteria of effectiveness. With his guidance such lists could be revised from time to time in order to help industrial pharmacists to decide which pharmaceutical products should be produced locally. In other words, the pharmaceutical producers must keep themselves informed on therapeutic needs continuously and at all times and not only during the stage of planning and establishment. It is a fact, well known and respected by the managements of modern pharmaceutical industries operating in industrialized countries that pharmaceutical products are in general short-lived, and that the production programme must be continuously adopted and changed, in consequence of the unceasing therapeutic progress, has to be taken into account. Though

there are drugs which for many decades (for example, acetylsalicylic acid phenobarbitone, digitalis glycosides, insulin) have been accepted as indispensable the majority will be replaced sooner or later by newer, more effective and less toxic ones, although the products which are replaced may actually have been of great importance and value.

3. Pharmaceutical Industry and Public Health Service

The European pharmaceutical industry estimates approximately 4 years for the development of one product. Such a product may stay on an average for 8 to 10 years on the market, but in the fifth year after marketing the sales often begin to decrease. (Müller-Haeseler, Zeit, 21 February 1969)

Pharmaceutical industries operating in developing countries, and especially those operating independently of research oriented foreign industries, will not, as a rule, have the chance to be the first on the market with their products and may start 12-15 years after the first delivery of such products. This period corresponds by and large to the duration of patent protection. This time-lag shortens the lifetime of their products greatly since evergreens are the exceptions and are produced by everyone. However, the chances for a local pharmaceutical industry to operate successfully even under these conditions, should not be estimated as being too small. A pessimistic outlook is not justified as long as these projects are not started as single purpose programmes on a crash basis. As long as they are integrated into the development of public health services in general, they are not operating in an isolated and therefore hazardous situation.

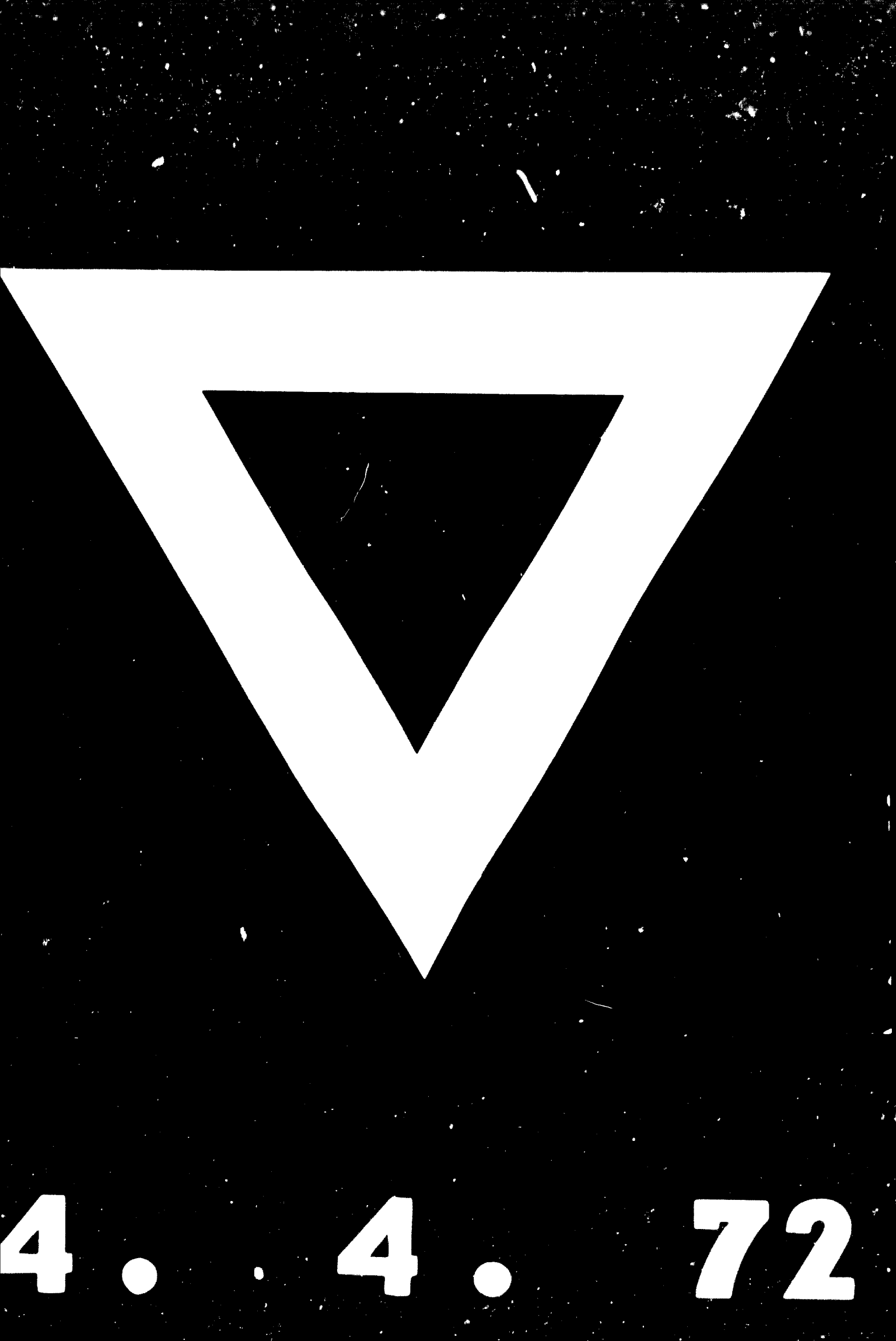
In conclusion it can be said that amongst the pre-requisites for a sound pharmaceutical production are, on the one hand, the permanent availability of specialists who can advise on therapeutic needs and progress, and, on the other hand, the existence of a number of public hospitals and pharmacies, large enough to provide a permanent minimum level of consumption of the pharmaceutical products produced by the newly established industry.

4. Technical Assistance by WHO

In the following, I would like to discuss briefly the services available in this context from WHO, and especially its Division of Pharmacology and Toxicology. Firstly, if specialists in therapeutics are not available locally, WHO fellowships could provide the training of such local specialists abroad. Secondly, if the thorough study of the therapeutic needs of an area, in which the establishment of pharmaceutical industry is planned, cannot be performed because of lack of local specialists, consultants could be made available through WHO. Thirdly, the units of Drug Safety, Drug Monitoring and Drug Dependence of the WHO Headquarters could provide, on request, written or printed information on special questions of drug therapy. They could support the medical advisers to such an industry with special literature and, by such, improve the ability of the medical advisers to draw their conclusions on a scientifically sound basis. Though WHO, in accordance with its statutes, will not be able to make decisions regarding the selection of drugs for production or for the extension of the existing production lines, WHO will be able to work in this field like a clearing house, distributing pertinent information to governments,

governmental agencies and scientists in the service of governments. This proposed co-operation will have to be performed in close and permanent liaison with the Industrial Technology Division of UNIDO. When the last Executive Board of WHO studied the question of "Co-ordination with other organizations" it was stated that the type of projects which could be implemented would be based on the specific needs of the health services and include short or long-term advisers, fellowships and supplies and equipment in any form, necessary to meet the request of a government, taking into account the availability, both internally and externally, of human and financial resources.

The Division of Pharmacology and Toxicology of WHO Headquarters would be interested in establishing such services as far as its personnel and financial resources would permit. Such a co-operation would also provide for a feedback system from which WHO could collect valuable information as to the experience of industries in different countries.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