THE SELECTION OF DRUGS FOR CHEMOTHERAPY RESEARCH IN LEPROSY [1]

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Unlike the problem in the chemotherapy of most infectious diseases, and even of tuberculosis, that of the selection of drugs for clinical work in leprosy is beset with numerous difficulties of diverse nature.

The first difficulty arises from the inability of *Mycobacterium leprae* to grow on any artificial medium, and from the impossibility, at the present stage of research, of transmitting leprosy to any laboratory animal. This precludes both *in vitro* and *in vivo* direct screening tests such as those which culminated in the introduction of isonicotinic acid hydrazide in the domain of tuberculosis.

Recourse to experimental infections by means of *M. leprae murium* has proved quite unreliable, as is shown by the contrast between, on the one hand, numerous clinical observations of the low degree of efficacy in human leprosy of isonicotinic hydrazide as compared with the sulfones and thiosemicarbazones (1, 2, 15), and, on the other hand, reports upon the outstanding activity of isonicotinic hydrazide in murine leprosy (6, 8, 14). Using the intracorneal inoculation test, Goulding, Robson, and Rees (10) found from a comparative study of therapeutic effects in mice of 4,4′-diaminodiphenylsulfone, thiosemicarbazones, and isonicotinic hydrazide that the last-named substance was the only one to display activity. A similar discrepancy exists between the good therapeutic effects in animals (13) and the far less satisfactory clinical results obtained with streptomycin (7).

The second difficulty encountered arises from the unusual length of the treatment periods inherent in leprosy, which virtually precludes the use of drugs like streptomycin, with pronounced side-effects, or those which would rapidly bring about bacterial resistance. Nothing of course is known about the conditions under which the Hansen bacillus might develop drug-resistant strains, but judging from the speedy appearance of Koch bacilli resistant to isonicotinic hydrazide in the treatment of tuberculosis, this might well account for the poor activity of this drug in human leprosy.

A third difficulty is of an ethical and even economic nature. Results of the many large-scale investigations reported in recent years, and the

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unanimous opinion of field clinicians with whom the author conferred during an extensive visit to leprosaria in Asia last year, underline the great value of 4,4'-diaminodiphenylsulfone (DDS) as a powerful and economical weapon for the control of leprosy. This places a great responsibility on the research worker who ventures to propose alternative substances, inasmuch as such compounds would have to possess at least equal therapeutic qualities and at the same time offer some kind of superiority, in order to make worthwhile the replacement of a drug with which clinicians are already well acquainted.

An evaluation of the therapeutic activity of the various drugs so far employed, and consideration of the experimental results recently obtained in the chemical control of the growth of acid-fast microorganisms, point to the possibility of establishing a set of empirical rules for the selection of substances to be submitted for clinical work in leprosy, which would lessen the risk of disappointment and failure.

1. The first rule of selection would be that the prospective substance must possess notable tuberculostatic activity, assessed *in vitro* and *in vivo* against as many strains of *M. tuberculosis* as possible. Such activity is, indeed, displayed by all the drugs so far used with some measure of success in leprosy—cyclopentenic acids from chaulmoogra oil and their derivatives, the sulfones, and the thiosemicarbazones. This rule, however, is not sufficient in itself, as is proved by the relative failure of the two major antituberculosis drugs, streptomycin and isonicotinic hydrazide.

2. The second proposed selection rule derives from the assumption that notable leprocidal activity is present only in tuberculostatic substances which show at the same time definite fungistatic properties. Mayer (16) has drawn attention to the botanical relationship between mycobacteria and fungi belonging to the order Actinomycetales, and suggested that this relationship might cover biochemical analogies which could be made use of in the quest for antituberculosis compounds. Mayer, Eisman, and Konopka (17) did in fact recently find highly tuberculostatic substances in the group of thiocarbanilides, which at the same time display important fungistatic properties. Buu-Hoï and Xuong (3, 4, 5) arrived at similar results from a study of the relationship between the tuberculostatic activity and metal-chelating properties (*i.e.* the ability to bind metals in the form of complex molecules) of organic molecules. The biochemical analogies postulated by Mayer between mycobacteria and fungi could here be ascribed to the importance, in both of these botanical groups, of lipid biosyntheses, which are probably controlled by metal-containing enzymes. From that point of view the Hansen bacillus seems to be closer to the fungi than does the tubercle bacillus, as witnessed by the fact that from among all the antituberculosis drugs used in leprosy, the ones which give good results are those which display antifungal properties (4,4'-diaminodiphenylsulfone, thiosemicarbazones, cyclopentenic

acids from chaulmoogra oil and their derivatives). Again, streptomycin and isonicotinic hydrazide, which are not fungistatic (11), are but poorly effective. It is worth mention that these latter compounds are considerably less lipoid-soluble than the active drugs.

Table 1 classifies the drugs currently in use in tuberculosis and leprosy, from the standpoint of the selection rules outlined above.

TABLE 1.—*Activities of various drugs used in tuberculosis and leprosy.*

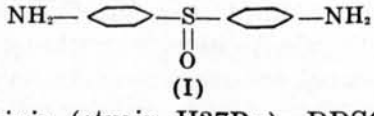
Drug	Tuberculostatic activity	Fungistatic activity	Solubility in lipids	Leprocidal activity
4, 4/-Diaminodiphenylsulfone	+	+	+	++
Thiosemicarbazones	++	+	+	++
Chaulmoogra derivatives/*a*	+	+	++	+
Streptomycin	+	0	0	Very poor
Isonicotinic hydrazide	+	0	Very low	Very poor
P–Aminosalicylic acid	+	0	0	0

a Although the over-all leprocidal activity of chaulmoogra derivatives is considerably less obvious than that of DDS, some forms of their therapeutic effect, such as the healing of dyschromic lesions of the skin, seem to be beyond question.

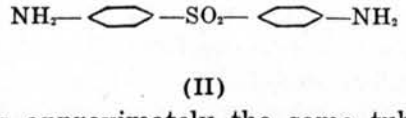
3. The third selection rule takes into consideration the necessity of long treatment periods, which factor demands drugs with as little toxicity and as few side-effects as possible. In this respect the toxicity of 4,4'-diaminodiphenylsulfone could be set as a standard which should not be exceeded.

4. The fourth selection rule derives from social considerations, and bears on the fact of the prevalence of leprosy among masses of population of very low standards of living. It is clear that any drug which cannot be manufactured easily and cheaply would not well serve our purposes, whatever its therapeutic merits. Here again it is useful to set the cost of 4,4'-diaminodiphenylsulfone as a standard of reference.

Experimental work in this Institute, carried out in the light of the considerations enumerated here, leads me to suggest that large-scale clinical studies be undertaken with compounds belonging to the sulfoxide group. One of these compounds, 4,4'-diaminodiphenylsulfoxide (I)—DDSO for the sake of brevity—seems particularly suitable for that purpose. In both *in vitro* and *in vivo* tests, using *M. tuberculosis var. hominis* (strain H37Rv), DDSO shows approximately the same tuberculostatic activity as 4,4'-diaminodiphenylsulfone (II). As regards com-



(I)



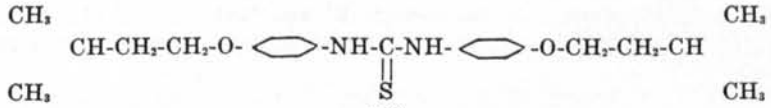
(II)

parative toxicities, the maximum tolerated dose of DDSO as determined in mice, when administered by mouth (9), is five times that of DDS (0.5 gm. per kilogram of body-weight, instead of 0.1 gm.). The long-range effects of DDSO on the blood system (on erythrocytes and hemoglobin) are less pronounced than with DDS. Experiments with volunteers have shown DDSO to be excellently tolerated in man at a dosage as high as 0.5 gm. per day for several consecutive days.

From the economic point of view, DDSO is at least as easy and inexpensive to prepare in large quantities in industry as DDS; actually, in certain chemical processes for the manufacture of DDS, the sulfoxide is obtained as an intermediate. The presence of two amine functions in the molecule of DDSO permits the preparation of a wide variety of mono- and disubstituted derivatives akin to those of DDS which have gained therapeutic importance (in particular the water-soluble compounds such as sulphetrone, diasone, or promin). The detection and determination of DDSO levels in the body fluids can be performed with methods very similar to those in use for DDS, for instance that of Schoog (18), based on diazotation and coupling with a derivative of α-naphthylamine. The difference in toxicity between DDS and DDSO is reminiscent of the behavior of the sulfone (III) and the sulfoxide (IV) derived from β,β-dichlorodiethylsulfide (mustard gas); the sulfone shares with mustard gas itself skin-irritant properties, whereas the sulfoxide is entirely innocuous (2).

(III) (IV)

Another group of compounds which merits close consideration is that of the lipid-soluble tuberculostatic and fungistatic thiocarbanilides. The mechanism of action of these compounds seems to differ from that of the sulfones, a fact which justifies their clinical testing in sulfone-resistant cases of leprosy. So far, we have made limited tests in Viet Nam with one such thiocarbanilide, 4,4'-diisoamyloxythiocarbanilide (V), the prep-



(V)

aration and chemical properties of which were recently reported (5). This compound showed no acute toxicity in mice up to a dose of 1 gm. per kilogram of body-weight, and no troublesome side-effects were observed on the pituitary and thyroid glands after prolonged administration. Good results have so far been obtained in three cases of tuberculoid leprosy resistant to disulone and chaulmoogra oil, and which were given a daily dosage of 0.1 gm. of compound (V) over a period of six months.

SUMMARY

1. The problem of the selection of new chemotherapeutic agents for clinical work in leprosy is discussed, and a set of rules for such a selection is proposed.

2. In the light of this discussion, certain new drugs, in particular the sulfoxides of the type of 4,4'-diaminodiphenylsulfoxide (DDSO), are suggested for large-scale clinical assay.

RÉSUMÉ

On étudie le problème de la sélection de composés chimiothérapeutiques nouveaux pouvant présenter un intérêt pour le traitement de la lèpre, et on propose un ensemble de règles permettant de tationaliser ce choix.

En application de ces règles, on suggère l'étude clinique sur une large échelle de certains composés tels que les sulfoxides du type du 4,4'-diaminodiphénylsulfoxide (DDSO).

RESÚMEN

Este es un estudio de los métodos de selección de nuevos agentes terapéuticos para el tratamiento de la lepra y los autores proponen ciertas reglas a seguir: 1—Oue la droga posea actividad tuberculostática, para poder hacer ensayos in vitro. 2—Se asume que una droga tuberculostatica es también activa contra la lepra. 3—Oue sea de poca toxicidad pues será necesario usarla por periódos prolongados. 4—Oue la droga sea fácil de preparar y no presente problemas económicos de gran magnitud.

Se desprende de ésta discusión que ciertos nuevas drogas, especialmente los sulfoxidos del tipo, 4,4' diaminodiphenylsulfoxido (DDSO) deben ser ensayados clínicamente en grande escala.

REFERENCES

1. Arguello Pitt, L. and Consigli, A. C. Nuestra experiencia con la hidracida del acido isonicotinico en el tratamiento de la lepra. VI Congreso Internacional de Leprología, Madrid, 1953 (abstract).
2. Buu-Hoï, N. P., Ratsimamanga, R. and Pacault, A. Sur le méchanisme d'action des substances du groupe du sulfure d'éthylène dichloré. Bull. Soc. chim. Biol. **27** (1945) 259-264.
3. Buu-Hoï, N. P. and Xuong, N. D. Sur les composés tuberculostatiques du groupe de la thiourée et leur mécanisme d'action. Compt. rend. Acad. Sci. **237** (1953) 498-500.
4. Buu-Hoï, N. P., Xuong, N. D., Binon, F. and Nam, N. H. Sur le mécanisme d'action des hydrazides tuberculostatiques. Compt. rend. Acad. Sci. **235** (1952) 329-331.
5. Buu-Hoï, N. P., Xuong, N. D. and Nam, N. H. Sur les acides hydroxamiques tuberculostatiques. Compt. rend. Acad. Sci. **236** (1953) 635-637.
6. Chang, Y. T. Chemotherapy of murine leprosy. II. The effects of streptomycin, sulfones and isonicotinylhydrazines on mouse leprosy. Internat. J. Leprosy **21** (1953) 57-71.
7. Chaussinand, R. Aspect actuel du problème thérapeutique de la lèpre. Bull. Soc. Path. exot. **44** (1951) 765-773; *reprinted* in Internat. J. Leprosy **20** (1952) 229-238.
8. Cruickshank, J. C. A trial of isoniazid in rat leprosy. Lancet **264** (1953) 624-625.

9. FOURNEAU, E., TRÉFOUËL, J., TRÉFOUËL, T., NITTI, F. and BOVET, D. Rapports entre constitution chimique et activité thérapeutique dans les séries des phénylsulfamide, diphénylsulfure, diphénylsulfoxide et diphénylsulfone. Bull. Acad. Méd. **118** (1937) 210-217.
10. GOULDING, R., ROBSON, J. M. and REES, R. J. W. Intracorneal murine leprosy and its response to isoniazid. Lancet **264** (1953) 423-424.
11. KIMMIG, J. and RIETH, H. Antimykotica in Experiment und Klinik. Arzneimittelforschung **3** (1953) 267.
12. LATAPÍ, F., BARBA RUBIO, J., RODRIGUEZ, O., ESTRADA, S. C. and BAEZ, M. M. Isoniazide en lepra. VI Congreso Internacional de Leprología, Madrid, 1953 (abstract).
13. LEVADITI, C. and CHAIGNEAU-ERHARD, H. Activité antimicrobienne de la streptomycine, de l'acide p-aminosalicylique et de la diaminodiphénylsulfone chez les souris contaminées par le bacille de Stefanski. Compt. rend. Soc. Biol. **145** (1951) 328-330.
14. LEW, J. and CARPENTER, C. M. The suppressive effect of isoniazid in murine leprosy. VI Congreso Internacional de Leprología, Madrid, 1953 (abstract).
15. LOWE, J. Isoniazid in leprosy. Lancet **263** (1952) 1012-1013.
16. MAYER, R. L. Recherches sur la chimiothérapie des mycoses et de la tuberculose. Revue méd. France (1941) Nov.-Dec., p. 3.
17. MAYER, R. L., EISMAN, P. C. and KONOPKA, E. A. Antituberculous activity of substituted thioureas. Proc. Soc. Exper. Biol. & Med. **82** (1953) 769-774.
18. SCHOOG, M. Diaminodiphenylsulfon, Nachweis und Blutspiegel. Arzneimittelforschung **2** (1952) 512.