ORIGINAL PAPERS PRESENTED AT THE COLLOQUIUM

1. Chemotherapeutic Trials in Leprosy, their Design and Assessment

Lepr, Rev. (1975), **46** (Suppl.), 9-16

The Role of WHO in Antileprosy Drug Trials

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The qualities and limitations of the drugs used in the treatment of leprosy are briefly outlined.

The need for primary prevention tools as against present secondary prevention (chemotherapy) methods is stressed.

In the absence of effective primary prevention, the prospects of improving the present antileprosy chemotherapy are considered and the past and present WHO drug trials reviewed.

The need for further efforts and future participation by WHO in drug trials is discussed.

WHO's Fifth General Programme of Work (1971), covering the period 1973-1977 inclusive, refers to leprosy as a communicable disease of major public health importance. In Africa (exclusive North Africa), the Americas and Asia, governments of developing countries considered leprosy, among other diseases, as a public health problem in 1957-1960 and again in 1965-1968 (Cockburn and Assaad, 1973).

To reduce progressively the prevalence of the disease, its associated deformities, and the human suffering it causes, has been the immediate objective of WHO's involvement in leprosy. The long-term epidemiological objective is to achieve a progressive reduction of the disease incidence. The achievement of both objectives would obviously benefit enormously from effective tools for primary, as opposed to presently available, secondary prevention methods.

Table 1 shows a secondary prevention method, chemotherapy, as the main pillar at our disposal to gain control of the disease, and explains the priority given by WHO to collaborative and research promoting activities in this sector, involving laboratory and clinical drug trials, to be followed closely by epidemiological investigations aimed at achieving primary prevention. Full attention will be paid by WHO, as an international organization, to the need for strengthening this type of research in the leprosy endemic countries themselves.

So much for the justification of WHO's role in promoting study and research in the chemotherapy of leprosy. The first successful use of sulphones by Faget (1943) as effective antileprosy chemotherapy was the most dramatic event

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TABLE 1

		Means and Measures	Programme Feasibility	Objective
1. Primary Prevention	1.1	Improvement of socio-environmental and other epidemiological risk factors	Investigations on nature of such factors in progress. Output promising, against natural decline in 100–200 years	LEPROSY CONTROL Progressive reduction of *Myco. leprae* transmission
	1.2	Specific antileprosy vaccination	Investigation proposed on vaccine development	
2. Secondary Prevention	2.1	Segregation	Impractical	
	2.2	Chemoprophylaxis	Of very limited public health value. Long-term protective value doubtful	
	2.3	Chemotherapy	Available, economically feasible but slow. Improvement required. Expectations favourable. Drug trials in progress and extension proposed	

since the discovery of *Myco. leprae* by Hansen. The frequently heard criticism that dapsone has not had a significant impact on the world leprosy situation is as superficial and unfounded as blaming penicillin for not having controlled VD, or DDT for not having eradicated malaria.

From the public health point of view, although we are fully aware of the limitations of secondary prevention in controlling leprosy, it is a fact that dapsone does reduce initial bacterial positivity of regularly treated cases in about 50% of lepromatous cases within an average of five years and in over 90% of cases within ten years.

Table 2 illustrates this point, showing the findings of reputable authors.

Accordingly emphasis has to be placed on regularity of treatment. Among irregularly treated lepromatous cases, 40% as shown by Vellut (1969) remain bacteriologically positive even after ten years of dapsone therapy.

Therefore, where dapsone is regularly taken, we do have a reasonably effective tool against the disease. On the other hand, the increasing importance of dapsone resistance, a greater danger to existing control efforts than the slow-acting property of dapsone, has been demonstrated in laboratory animals and in man (Pettit and Rees, 1964; Pettit *et al.*, 1966; Adams and Waters, 1966; Shepard *et al.*, 1969, and others). The real extent of dapsone resistance, specifically in long-term control programmes, is not known and requires urgent investigations by all concerned including WHO, which could coordinate such studies.

It is only logical to look out and search for alternatives to dapsone, and the desirable properties that a drug (drugs) for the treatment of leprosy should possess are:

(1) Effectivity in rapidly suppressing clinical and bacteriological activity in the large majority of cases;
(2) Good tolerance, excluding serious side-effects and keeping drug induced reactions at a minimum;
(3) Negligible or non-existent development of resistance by *Myco. leprae* in the course of treatment, thus ensuring long-term results and a low proportion of reactivations;
(4) Simplicity of administration, especially if the drug is to be used in mass treatment.

In Table 3 we have listed, together with their main characteristics, four drugs currently in use, possessing to a significant degree the already mentioned properties as measured by clinical and bacteriological improvement of cases.

These drugs have been chosen as being the ones about which the most information is available. Other drugs such as isoniazid, thiosemicarbazone (TBI), streptomycin, long-acting sulphonamides, etc., have not been included because their use in field programmes has been rather limited, or they have to be used with exceptional caution.

We shall now briefly review the role of WHO vis-à-vis antileprosy drug trials in the past, present and future.

In the WHO Programme of Leprosy Research, the evaluation of anti-leprosy drugs has been carried out in the following centres:

(1) Central Leprosy Teaching and Research Institute, Chingleput, India (from 1962 to the present);
(2) Instituto Nacional de Dermatologia, Ministry of Health, Caracas, Venezuela (from 1960 to the present);
(3) Institut Marchoux, Bamako, Republic of Mali (from 1960 to the present);
(4) Sanatorio-Villaggio Isola Alessandra, Gelib Giuba, Somalia (from 1968 to the present);
(5) Institut de Lèprologie appliquée, Dakar, Sénégal, (from 1971 to the present);
(6) Leprosy Service Research Unit, Uzuakoli, Eastern Nigeria (form 1960 to 1964);
(7) Colonia Sanatorio San Francisco de Borja, Fontilles, Alicante, Spain (from 1965 to 1968);
(8) Lucha Dermatologica, Buenos Aires, Argentina (from 1965 to 1967).

Drug trial centres collaborating with WHO have some difficulty in following the requirements of WHO-Controlled Clinical Trials (Doull, 1960), and the number of untreated lepromatous patients available at these centres usually has been inadequate. Often an independent appraisal before therapy, at intervals throughout the study, and at the end of the trial, could not be undertaken owing to insufficient funds. Without going into details of results obtained, drugs or drug regimens which have been investigated are:

Different brands of repository dapsone;
Diethyl-dithiol-isophthalate;*
Methimazole or Tapazole, an antithyroid drug;
Two different long-acting sulphonamides (Ro 4-4393 and Sultirene);
Injectable DPT

* Ditophal, Etisul.

TABLE 2

Author[a]	Year	Country and area	Years of observation	Weekly Dapsone dosage in mg	Regularity of attendance	Number of bacteriol. positive (L/B) cases	Annual reduction of bacteriol. positivity % of remaining positive cases									
							1	2	3	4	5	6	7	8	9	10
Lechat, M.[1]	1961	Congo Yonda	9	800	"regular"	1254	100	56	37	27	21	14	9	6	3	
		Nigeria North			0-75% +	1187	65				18					
		Nigeria South			75% +	664				20						
		Thailand			50-74%	73				35						
		Khon Kaen			25-49%	27				66						
Patwary *et al.*[2]	1963	Cameroun	5	?	0-24%	13				92						
Quagliato *et al.*[3]	1970	Brazil Campinas	10	400 to 600	75% +	690	82	71	55		31				9	3
					"irregular"	125	80	73	72		55				26	17
Basto, P. and Barbosa, A.[4]	1968	Portugal Tocha	10	600	?	155										8
Vellut, C.[5]	1969	India Tamil Nadu	10	400 to 600	75% +	595			80		32					5
					"irregular"	705										40

[a] 1-5 Rearranged data.

TABLE 3

Antileprosy drug (nonproprietary name)	Chemical name	*Myco. leprae* resistance	Tolerance	Other undesirable effects	Cost
Dapsone	4,4′-diaminodiphenyl-sulphone	Yes, extent unknown probably not under 5 years of treatment	Fair to good	–	Low
Clofazimine	Rimino-phenazine compound 3-(*p*-chloroanilino)-10-(*p*-chlorophenyl)-2,10-dihydro-2-(isopropylimino) phenazine	?	Good	Skin pigmentation	Moderate
Rifampicin	Antibiotic 3-[[(C 4-methyl-l-piperazinyl) imino] methyl] rifamycin SV	?	?	?	High
Thiambutosine	Diphenylthiourea 1-(*p*-butoxyphenyl)-3-(*p*-dimethylaminophenyl) -2-thiourea	Yes, frequent after 1-2 years treatment	Good	–	Moderate

Combination of drugs such as:

(1) dapsone + streptomycin + INH;
(2) dapsone + INH + PAS;
(3) dapsone + INH + TB1;
(4) dapsone + DPT;
(5) dapsone + Ditophal.

Most of these trials were initiated and terminated between 1962 and 1966. Results of all these trials, with regard to bacterial reduction, were not superior to those obtained with dapsone when given as a single drug (Bechelli and Martinez Dominguez, 1966).

The WHO Expert Committee on Leprosy (1966) recommended dapsone administration to be the basic treatment for field programmes.

Since 1966 other studies have been initiated and are, with the exception of the short-term thalidomide trial (Iyer *et al.*, 1971) still in progress. These are:

Multicentre studies on conventional and low dapsone dosage schemes (four centres);
Clofazimine and Aspirin or Thalidomide in lepra reaction (ENL), (three centres);
Controlled acedapsone trial (3 centres);
Dapsone chemoprophylaxis in children (two centres).

Future Orientation

Having stressed the need for the drug trials and reviewed past and ongoing activities, what is the most promising attitude for WHO to adopt in the immediate future, within its own limitations other than those obviously set by budgetary considerations, concerning laboratory, clinical and epidemiological trials of antileprotic drugs?

(a) The availability of a reliable and generally accepted test for determining under field conditions the viability of *Myco. leprae* in lesions. Previous research into the implications of the morphology of the bacillus, the mouse footpad technique, as well as the importance of the nose in the transmission of leprosy (Rees *et al.*, 1974) have paved the way for possible future developments in this field.

(b) The long periods of time required to achieve bacterial tissue clearance in lepromatous leprosy are common knowledge. The reasons for this slow removal of bacterial debris and a possible faster tissue clearance by increased immunoactivity need studies in animal models and in man.

(c) The search for new, safe and effective compounds, equally merits intensive research in infected animals and in patients.

(d) To explore further the advantages of combined drug therapy on the lines pioneered by Freerksen and colleagues (Freerksen and Rosenfeld, 1973), keeping in mind what has already been mentioned under desirable properties of antileprosy drugs.

(e) The ranking of established antileprosy chemotherapeutic agents in the order of their importance, evaluated from their safety point of view.

(f) The determination of drug resistance and its frequency in field control programmes is another urgent task, as well as practical measures to prevent the spread of dapsone resistant strains of *Myco. leprae*.

(g) Out-patient treatment of leprosy patients in preference to institutional care was for the first time recommended by WHO in 1953, and these recommendations were further extended to cover all forms of leprosy in 1966. In tuberculosis control, similar recommendations were made by WHO in 1959 and 1960 based on the results obtained in controlled studies in India, completed within one year. In contrast to the latter, in leprosy we still need a controlled comparison of institutional and domiciliary treatment. However, such studies would require follow-up periods of at least five years or more.

(h) Besides the search for new compounds which could be promising agents for safe, fast and effective chemotherapy, investigations in the field of immunotherapy should not be neglected. Attempts at immunotherapy have in the past chiefly consisted of the injection of peripheral leucocyte suspensions and leucocyte extracts, attempting to increase cell-mediated immunity in lepromatous leprosy. Areas for future research in the field of immunotherapy have been spelled out by the second WHO-convened meeting of immunologists in New Delhi (1973). In addition, the possibilities of increasing immuno-resistance by means of thymosin deserve appropriate investigations in animals and in man.

Constraints to our objectives which have to be taken into account are:

Ethical aspects: It is the responsibility of the institution and the principal investigator to safeguard the rights and welfare of human subjects involved in research supported in whole or in part by WHO, in accordance with the appropriate national code of ethics or legislation.

Regulatory requirements: It is the responsibility of the institution and the principal investigator to comply with national regulations pertaining to clinical studies of new drugs or devices.

Suitable Institutions for Drug Trials in Leprosy

In our opinion based on world-wide experience, the often expressed view on shortage of lepromatous patients for drug trials is only partially true. However, the number of well staffed and equipped institutions in countries which still have a relatively high incidence of lepromatous cases, needed for drug trials, is insufficient, whilst on the other hand several highly qualified investigators work in institutions and areas in which new lepromatous cases are becoming rare indeed.

Voluntary agencies supporting numerous institutions in nearly all leprosy endemic countries could expand their programmes and coordinate their relevant efforts with WHO. Thus more centres could participate in drug evaluation studies, the results of which would ultimately be of benefit to world-wide leprosy control efforts.

Several centres carrying out excellent research work in antileprosy drugs have not, so far, established any kind of link with WHO. It would be beneficial for private or national institutions involved in leprosy research, as well as for WHO, to develop without delay and with no implications of financial support or of any sort of commitment from the participants, a regular exchange of information about current investigations in leprosy therapy. It is felt that WHO with its various specialized units on drug evaluation and classification, pharmacology, cancer, immunology etc., including the WHO panel of experts, could probably serve as an objective forum.

Not confining ourselves to WHO activities in leprosy drug-research, a word

about the general allocation of resources to this field seems pertinent. To compensate for a diminishing interest on the part of the pharmaceutical industry in the search for new drugs against tropical diseases in general and leprosy in particular, an appeal is made for the pooling of resources to rationalize drug development. In a world with so many factors of financial instability at work, the mobilization of additional resources for drug development and trials is necessary to ensure further progress.

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