DDS and Malaria

The treatment of malaria by quinine is perhaps the prototype of successful chemotherapy. Remarkable as it has been in its results, however, physicians have never been satisfied with its efficacy, and for many years investigations have been in progress in the effort to discover still more effective specific antimalarial chemicals. Out of this continued research have come atabrine, chloroquine, primaquine and related drugs. The search goes on, accelerated from time to time by the recognition of new problems in the treatment of malaria.

During World War II, when malaria was a grave problem in the military forces in the islands of the South Pacific, and other parts of the world as well, the antimalarial effect of literally thousands of chemical compounds was investigated by research organizations in the warring countries. The antibiotics and sulfa drugs that had proved so successful in the treatment of bacterial infections were naturally among the earliest to be studied. Not surprisingly, the sulfonamide sulfanilamide was one of the first drugs actively investigated. Its remarkable record in a wide spectrum of bacterial diseases was good reason for its trial in other forms of infectious disease. A natural sequel of the investigation of the sulfonamides in malaria was a study of the closely related sulfones.

Even before these war-stimulated studies were in progress, malariologists had made pioneer investigations of the sulfa drugs in experimental malaria. In the late 1930's and early 1940's numerous studies of this character were reported, and trial of the compounds studied was soon extended to malaria in man. Apparent successes and apparent failures were reported.

Coincidentally, and for very much the

same reasons, the efficacy of the sulfonamides and sulfones in mycobacterial diseases was being investigated. Researches on tuberculosis by Feldman, Hinshaw and associates pioneered among these. Coincidentally, studies of the effect of sulfones on leprosy and leprosy-like diseases were underway. Doull[1] made a painstaking review of these, with which readers of THE JOURNAL are familiar. Among the reports taken up in detail by Doull was the classic paper on the chemotherapeutic effect of promin on clinical leprosy by G. H. Faget and associates, which was reprinted in the preceding issue of THE JOURNAL.[2] As is well known, the toxicity and inconveniences in the use of promin and other substituted sulfones led before long to the use of the parent compound, diaminodiphenylsulfone, or DDS[3], which soon became the standard drug in the treatment of leprosy. The pioneer work of Cochrane and associates in India, who used parenteral routes for the drug, Souza Lima in Brazil, Lowe and Smith in Nigeria and Floch and Destombes in French Guiana, who initiated oral use, started DDS on its long course and a wide use that has extended to a great many thousand leprosy patients.

Leprosy and malaria are coincidentally endemic in many parts of the world. Inevitably, therefore, many leprosy patients have been treated with antimalarial agents, and many malarial patients with antileprosy drugs. From time to time a suggestion of cross therapeutic action has been reported. The first of these to which some prominence has been given, was a report by D. L. Leiker[4], at the time Chief of the Leprosy Control Division of the Department of Health in Netherlands New Guinea. Leiker noted that malaria was rare among DDS-treated patients in a leprosarium in an area in which malaria was endemic in the general population. Other reports of similar import have appeared, notably one by H. M. Archibald and the leprologist C. M. Ross[5] in Nigeria. Not much attention has been paid to these reports, however, until recently, when the treatment of malaria by conventional methods has again run into difficulties, as a result this time of the development of strains of *P. falciparum* resistant to standard antimalarial drugs. This complication, also brought to the fore by military operations, this time in southeast Asia, and in particular in Viet Nam, has led to renewed search for effective antimalarial drugs. Old results with the sulfones have been recalled and new studies on their action have been initiated. Out of several on this subject two are cited here[6, 7] to point up the direction of studies and possible fruitful results to be anticipated.

The significance of the studies reported in these two papers, each of which was carried out among volunteering penitentiary prisoners, is the same, viz., that DDS is effective against experimental human infection by strains of *Plasmodium falciparum* that are resistant to conventional antimalarial drugs. The effective action is apparently most readily evident when DDS is administered together with some other types of antimalarial agents. How effective DDS and related drugs will eventually prove to be depends, of course, on thorough

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[1]Doull, J. A. Sulfone therapy of leprosy. Background, early history and present status. Internat. J. Leprosy **31** (1963) 143-160.

[2]Faget, G. H., Pogge, R. C., Johansen, F. A., Dinan, J. F., Prejean, B. M. and Eccles, C. G. The promin treatment of leprosy. A progress report. Publ. Hlth. Rep. **58** (1943) 1729-1744. *Reprinted* in Internat. J. Leprosy **34** (1966) 298-310.

[3]For details of its rapid initiation in different countries see Doull, J. A., *loc. cit.*, and Bushby, S. R. M. *In* Leprosy in Theory and Practice. Cochrane, R. G. and Davey, T. F., Eds. Bristol, John Wright & Sons, Ltd. and Baltimore, Williams and Wilkins Co., 2nd ed., 1964, 344-370.

[4]Leiker, D. L. Note on sulphone activity in malaria infection. Leprosy Rev. **27** (1956) 66-67.

[5]Archibald, H. M. and Ross, C. M. A preliminary report on the effect of diaminodiphenyl sulfone on malaria in northern Nigeria. J. Trop. Med. & Hyg. **63** (1960) 25-27.

[6]Degowin, R. L., Eppes, R. B., Carson, P. E. and Powell, R. D. The effects of diphenylsulfone (DDS) against chloroquine-resistant *Plasmodium falciparum*. Bull. WHO **34** (1966) 671-681.

[7]Aviado, D. M. Pharmacology of new antimalarial drugs. I. The sulfones. Unprinted. Issued as a progress report in a study carried out under contract with the Medical Research and Development Command of the U. S. Army. This preliminary report lists 311 references. *In press*, Proc. Third Internat. Pharmacol. Congr. Pergamon Press, Oxford, 1967.

trial. Field trials are under way, and preliminary reports should be available shortly.

An opportunity lies open to leprologists to contribute to this new quest for knowledge. Many carefully kept records on DDS-treated persons are at hand. One thinks, for example, of the several large studies on the prophylactic use of DDS. Hundreds of apparently healthy contacts have been treated with DDS in India and Korea with the hope of preventing leprosy; attention has been drawn to these studies from time to time in THE JOURNAL[8]. In addition to these are the thousands of records of leprosy patients treated with DDS in leprosaria and outpatient clinics all over the world. Is it possible to determine the annual incidence and prevalence of malaria in such selected populations in comparison with rates in the general population.

Also leprologists should be able to add to information on the possible value against malaria of other antileprosy agents, such as the long-acting sulfonamides, the phenylthioureâs, diethyldithiolisophthalate, and numerous other drugs reported as of more or less value in leprosy.

As a matter of fact there is no reason for limiting studies of this character to malaria and leprosy. Other diseases than malaria coexist widely with leprosy in many areas, and proper epidemiologic and statistical evaluation of DDS-treated contacts and patients might possibly yield surprising dividends for other diseases.

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[8]See, for example, with respect to the two studies named, Yoshie, Y. Editorial. The United States Japan Leprosy and Tuberculosis Conference. Internat. J. Leprosy **34** (1966) 311-313.