

The Chemoprophylaxis of Mycobacterial Diseases

With the development of effective specific chemotherapy for treating a number of diseases, the use of chemotherapeutic agents to prevent the development of diseases in exposed populations has become an accepted procedure, and one widely practiced. The prolonged use of Atabrine for the prevention of malaria, and of certain sulfa drugs for the prevention of venereal disease, were conspicuous examples of the practice during World War II. The later recognized superior value of chloroquine and amodiaquine for the chemoprophylaxis of malaria, and of penicillin for venereal disease, are well known. Possibly less generally known, but apparently at least as effective, is the prophylactic administration of Pentamidine and other trypanocidal agents for the prevention of African trypanosomiasis.

In estimating the effectiveness of chemoprophylaxis through the use of chemotherapeutic agents of proven value in the treatment of disease, what is meant by prophylaxis must be defined carefully. By and large the term is used, with some overlapping, in two senses: (1) as true chemotherapy to prevent the progression of an established actual, but early microbial disease from a latent to a clinically progressive form, and (2), more precisely, totally to prevent the primary establishment of the microbial disease by preventing multiplication of the offending germs from the outset.

In the field of mycobacterial disease chemoprophylaxis has been practiced in these two respects for more than a decade. Recent reports on studies sponsored by the World Health Organization on the chemoprophylaxis of tuberculosis, published in that organization's *Chronicle*,¹ describe (1) investigations instigated by R. Debré and carried out under the aegis of the Institut Nationale d'Hygiène (now the Institut Nationale de la Santé et de la Recherche Médicale) in Paris, and (2) work at the

Tuberculosis Chemotherapy Centre in Madras, under the joint auspices of the Indian Council of Medical Research, the Madras State Government, the Medical Research Council of Great Britain, and WHO. Data are presented briefly also for investigations by a WHO-assisted tuberculosis chemotherapy pilot scheme in Kenya and studies by Czechoslovak public health teams in cooperation with WHO.

In these several studies the known effective tuberculostatic drugs streptomycin, para-aminosalicylic acid, and isoniazid have been used, with generally favorable results. By 1960 the French study had "demonstrated definite value of early treatment with drugs in reducing the overall incidence of post-primary manifestations of tuberculosis in children and adolescents."² Drug treatment within two years after the tuberculin test first became positive was considered especially effective in preventing serious tuberculous complications.

Numerous other studies are under way, of which only one, in the interest of economy of space, will be mentioned here. This is a large cooperative enterprise started in 1955 by the U.S. Public Health Service, in which a "double blind" control system, involving the use of isoniazid and placebo pills, has been followed out for ten years with continuous statistical supervision. These studies, by Ferebee, Mount, Comstock and associates, have shown a consistently favorable trend in preventing the development of clinically significant tuberculous complications among (1) previously uninfected (tuberculin-negative) contacts, and (2) persons with clinically recognizable but apparently latent, initially non-progressive tuberculous lesions. Recently Ferebee³ has drawn up an "epidemiological model of tuberculosis in the United States" in which the possible roles of (1) isoniazid

¹ WHO-assisted activities, in tuberculosis. WHO *Chronicle* **19** (1965) 365-374. The chemoprophylaxis of primary tuberculosis. *Ibid.* 375-377.

²See LOTIE, A. and ROUILLON, A. *Bull. Inst. nat. Hyg. (Paris)* **15** (1960) 713.

³Presentation at meeting of the International Union against Tuberculosis, Munich, Germany, October 2, 1965.

prophylaxis in persons recognized as infected by tuberculosis (on the basis of U.S. Public Health Service studies) and (2) BCG vaccination of uninfected persons (on the basis of the well known British experience in that field) are compared. A substantial saving in morbidity by the former procedure is calculated.

In further reference to the same program of studies Comstock and Palmer⁴ have stated their conclusions as follows: "Some treatment of apparently healthy harborers of tubercle bacilli will be needed for effective prevention. At present the only hopeful procedure is chemoprophylaxis. Treatment of healthy persons with isoniazid has been shown to cut tuberculosis rates by more than half for a period of several years. Although a decrease in tuberculosis of even this magnitude among reactors could be a major contribution to tuberculosis control, it is clear that chemoprophylaxis is still in its infancy. Little is known of the optimal dosage or treatment schedules for isoniazid, the only drug to have been tested for prophylaxis."

As a result, however, of such and many other studies in course throughout the world there is now increasing use of isoniazid prophylaxis in the private practice of medicine as a preventive measure against contagion among household contacts of known open tuberculous cases.

With respect to the other widely spread mycobacterial disease, leprosy, studies of specific chemoprophylaxis are under way. It is generally admitted that the chemotherapy of leprosy is less rapidly effective than that of tuberculosis. Nevertheless, there is general agreement that 4,4' diaminodiphenyl sulfone (DDS, dapsone, and other terms) is a drug specifically active against the presumptive mycobacterial agent of the disease, *M. leprae*. As such its use in chemoprophylaxis is logical, and several studies, following pioneer investigations of Figueredo and co-workers in this field, are on record.

During the past few years preliminary reports on a large study carried out by collaboration between the Central Leprosy Teaching and Research Institute at Chingleput and the Indian Council of Medical Research (with a small subsidy from WHO) have been made. Recently a formal "interim report" has been published, which gives promising indications of what may be expected by this procedure in leprosy.⁵ The work covered by the interim report, planned by the Indian Council of Medical Research in 1960, involved selection of an area with a high leprosy prevalence rate, a high rate of lepromatous leprosy, a substantial number of healthy child contacts, and the formation of two comparable study groups: (1) a prophylaxis group (receiving DDS) and (2) a control group (receiving a placebo). Periodic reviews were projected, with a final assessment after five years.

The Central Leprosy Teaching and Research Institute was selected as the operating organization, because of the adequacy of its staff and facilities and its adjacency to a region of environmental conditions required for a suitable study. The population ultimately included was more than 200,000, residing in 381 villages in an area of 325 square miles. The total number of leprosy patients detected was 4,370, giving an overall prevalence rate of 21 per 1000. The lepromatous rate was 14.3 per cent. The number of contacts under 15 years of age was 732; 672 "source cases" were recognized as such.

The investigation was carried out by the "double blind" method; the paramedical workers administering the tablets, the medical officers examining the contacts, the "source" patients themselves, and the contacts, were all ignorant as to which were treated patients and which were controls. The latter knowledge was available only to the headquarters staff. Detailed supervision in the field was given by paramedical workers, who ensured that subjects in

⁴ COMSTOCK, G. W. and PALMER, C. E. Long-term results of BCG vaccination in the southern United States. *American Rev. Resp. Dis.* **93** (1966) 171-183.

⁵ DHARMENDRA, MOHAMED ALL, P., NOORDEEN, S. K. and RAMANUJAM, K. Prophylactic value of DDS against leprosy—an interim report. *Leprosy in India* **37** (1965) 1-20.

the study actually took the specified pills. Periodic examinations of patients and contacts were made by designated medical officers. The results of two and a quarter years of study are covered in the interim report. As might be expected, some depletion in the number both of source cases and of contacts took place during the period of investigation, but the great majority, ensuring a substantial number for study, remained.

While it is too early to place full confidence in the initial results as an index of future findings, the first results reported are encouraging. During the period of observation 43 cases of leprosy were recorded among 585 contacts. Of these, 14 were among 291 contacts in the prophylaxis group and 29 among 294 contacts in the control group; the difference was calculated as statistically significant at the 2 per cent level. It was therefore concluded tentatively, that the routine administration (twice a week) of DDS to healthy child contacts of leprosy patients was protective.

Interesting facts were that the protective value first became apparent only after nine months of treatment and that it seemed much greater in children under 10 years of age than in the older age groups. The importance of the latter apparent fact is practical prophylaxis is obvious. Further studies are in progress. Final judgment is reserved. But results thus far have engendered some optimism.

In all reports of which the Editor is aware a good deal of caution is expressed in forming final conclusions in the long-term use of chemoprophylaxis. All authors in the mycobacterial field, which includes both tuberculosis and leprosy, while encouraged by short-term results, are less committal about long-term success. Year-in-year-out drug taking is a far from normal existence. Its ultimate repercussions cannot yet be told. Cumulative toxicity is possible. There may be interference with the normal development of natural immune and presumptively protective processes. The present discrepancy in results between treated and control groups may not hold up. Finally the psychic impact of continuous drug taking as a means of warding off a supposed ever present danger cannot be ignored. The difference between that kind of prophylactic treatment and a one-shot preventive measure such as that involved in vaccination is easily seen.

Fortunately these difficulties are never overlooked. Time will settle many of them. New leads inevitably will develop in such programs as that here briefly described. Readers will await further reports from Dharmendra and his colleagues with interest.

E. R. LONG