Duration of Specific Treatment in Leprosy

The advent of effective specific chemotherapy for leprosy in the form of the sulfone drugs very quickly provided a new set of problems deriving from the slowness of response to these therapeutic agents and related to the chronicity of leprous infection. Prominent among these have been questions of how long therapy should be continued before the patient becomes noninfective, how long therapy should be continued in order to assure a minimum number of relapses and, indeed, to achieve a "cure." Very early in the experience with this treatment it was evident that clinical evidence of improvement preceded laboratory support of this conclusion, but that within weeks morphologic changes could be detected in bacilli which suggested their deterioration and probable decrease of already modest virulence and invasive powers. In due course refinement and extension of these observations led to the development and extensive use of the Bacteriologic and Morphologic Indices (BI and MI respectively) as measurements and records of the effectiveness of therapy and of therapeutic progress. Clinical observations as well as the witness of contrasting consecutive BI responses in various patients under treatment very soon gave evidence that therapeutic response was not uniformly predictable because of wide variations in the individual patient responses. That there would be relapses was readily predictable from experiences with other chemotherapeutic agents and other pathogens, but it was not till 1950 that the first instance was recorded by Erickson.[1] Subsequently a number of confirming reports appeared, among them the recent ones by Browne[2, 3] and by Hastings *et al.*[4] As might also be expected, some instances of relapse have been attributable to the development of true sulfone-resistant *Mycobacterium leprae;* but not all are so explainable and perhaps a greater number of relapses can be related to inadequate duration and amount of therapy. Since such relapses occur among patients on outpatient treatment as well as those living in leprosaria, it seems evident that they are often true endogenous re-exacerbations rather than instances of reinfection.

The Morphologic Index has been largely accepted as a measure of the effect of chemotherapy on bacilli; specifically as being a morphologic indication of the pro-

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1 Erickson, P. T. Relapse following apparent arrest of leprosy by sulfone therapy. Publ. Hlth. Rept. **65** (1950) 1147-1157.

2 Browne, S. G. Dapsone resistant *Mycobacterium leprae* in a patient receiving dapsone in low doses. Internat. J. Leprosy **37** (1969) 296-301.

3 Browne, S. G. Relapses in leprosy, Uzuakoli Settlement. 1958-1964. Internat. J. of Leprosy **33** (1965) 273-279.

4 Hastings, R. C., Trautman, J. R. and Mansfield, R. E. Further observations on streptomycin combined with sulfones in relapsed lepromatous leprosy. Internat. J. of Leprosy **37** (1969) 130-134.

portion of remaining probably dead to probably viable pathogens. Though such morphologic changes in bacilli have been noted in many laboratories and have been regarded as evidence of deterioration, if not death, of the bacilli, the electron microscopic studies by Rees and Valentine[5] did much to initiate the concept. A recent report by Shepard *et al.*[6] followed successive samples of *M. leprae*, from six patients under treatment, for their ability to initiate growth in the foot pads of mice. No growth was obtained from any patient bacillary sample after 180 days of therapy with DDS. We have frequently heard this report cited as if the study indicated that it can be assumed that in most patients the bacilli are essentially all dead after equivalent therapy, though the investigators did not so claim. Certainly the many relapses occurring after many months and years of treatment speaks for caution regarding such an interpretation. Valuable as the foot pad technic has been, it must be born in mind that it represents a limited, slow and apparently difficult growth of bacilli in an essentially unfavorable host. Furthermore, no comparative technics have yet become available which might serve as a check against the foot pad technics, except for the mycobacterial growth produced in thymectomized, irradiated mice by Rees.[7] The latter technic is too new and difficult to have been of practical value as a control assessment technic for the foot pad results. Therefore, there is no firm assurance that morphologically altered bacilli which will not grow in the mouse foot pad may not be capable of regeneration and growth in the more favorable human host. A growing recognition of the significance of widespread lesions in the reticuloendothelial system as well as many viscera additionally raises the question as to whether or not a few skin samples can be considered representative of the status of the disease and the bacillary population. The low temperature growth requirement hypothesis with respect to *M. leprae* is beset by too many doubts to admit the contention that bacilli in internal organs are nonviable, or even less virulent and more sluggish than those residing in the skin.

These, and other considerations, illustrate the shaky foundation for clinical judgment in answering the pressing question of how long to continue treatment, most particularly in the lepromatous patient. Therefore, it is not remarkable that many, *vide* Cochrane[8, 9], have promulgated the concept that therapy should continue for the duration of the patient's life. This concept is impractical in that it is unlikely to be followed by patients young enough to have a considerable life expectancy and who, when they regard themselves as cured, will wish to disassociate themselves from the stigma of leprosy in every possible way. For some it may be dangerous on the general principle that any long term introduction of a drug into the human biologic mechanism may result in unforseen and unknown consequences. It is undesirable in that it inadvertently contributes to the ages old opprobrium associated with leprosy by implying that this disease is dangerous beyond most others, for there are few, if any, other infectious diseases for which a life-long sentence to treatment is advocated.

For at least a decade and a half additional pertinent information bearing on this problem has been available but little recognized, discussed or practiced in this connection. Its essence is summarized in Figure 1. The very variance noted above in patient response under treatment provides its basis and the BI response its measure.

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5 Rees, R. J. W. and Valentine, R. C. The appearance of dead leprosy bacilli by light and electron microscopy. Internat. J. Leprosy **30** (1962) 1-9.

6 Shepard, C. C., Levy, L. and Fasal, P. The death of *Mycobacterium leprae* during treatment with 4,4'-diaminodiphenylsulfone (DDS). Initial rates in patients. American J. Trop. Med. & Hyg. **17** (1968) 769-775.

7 Rees, R. J. W. Enhanced susceptibility of thymectomized and irradiated mice to infection with *Myco. leprae*. Nature (London) **211** (1966) 509, 657.

8 Cochrane, R. G. Prognosis and criteria of discharge. *In*: Leprosy in Theory and Practice. R. G. Cochrane and T. F. Davey, Eds. Bristol, John Wright & Sons, Ltd.; Baltimore, Williams and Wilkins, Co., 2nd ed. 1964, p. 574.

9 Bushby, S. R. M. Chemotherapy. *In*: Leprosy in Theory and Practice. R. G. Cochrane and T. F. Davey, Eds. Bristol, John Wright & Sons, Ltd.; Baltimore, Williams and Wilkins Co., 2nd ed. 1964, p. 355.

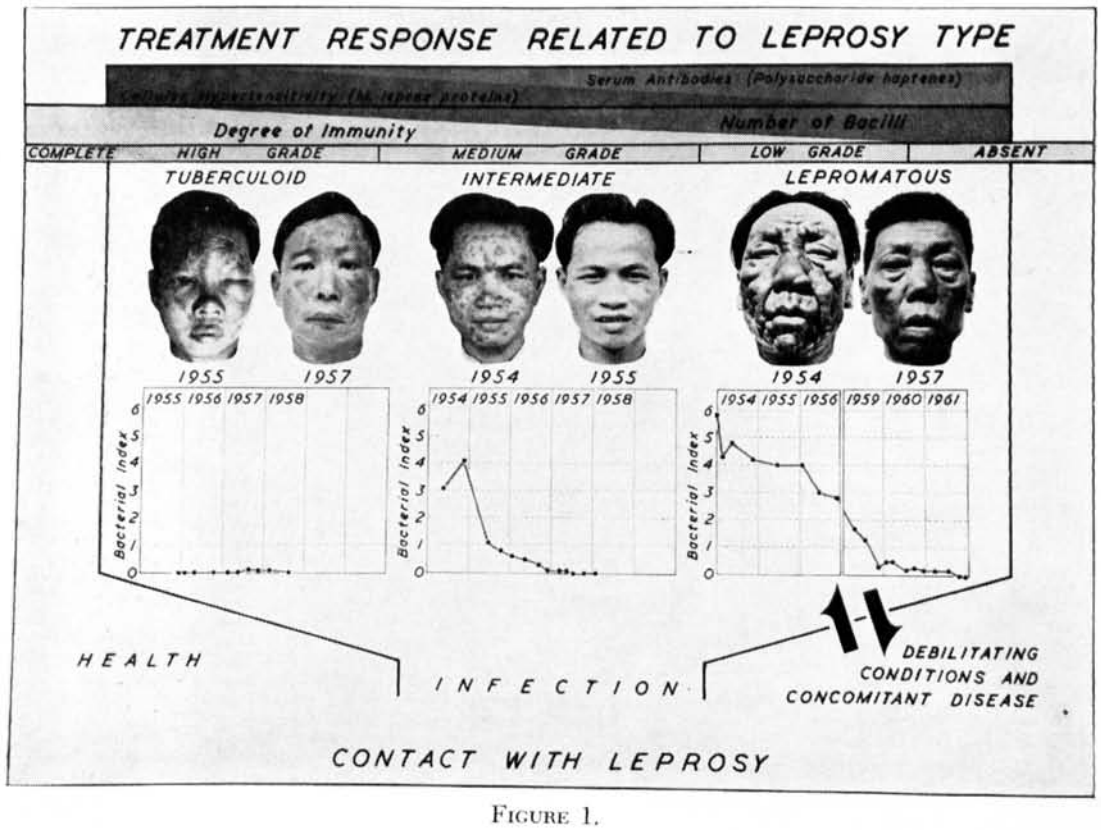

FIGURE 1.

The BI is the key, rather than the MI, for the former reflects the host's ability to dispose of the pathogen, whether or not the pathogen can be recognized as being viable. This reflects more truly the host capabilities in coping with the total pathogen disposal.

The therapeutic principle consists in continuing therapy in any given patient for as long after his BI becomes negative as it took to achieve negativity in that particular patient. Some patients, notably tuberculoid, have a negative BI while displaying active disease. In these, disappearance of clinical and histopathologic evidence of disease activity may be substituted for the BI in determining the period in which apparent cure was achieved.

The purpose of continuing therapy after the BI becomes negative is well known, since it is generally recognized that this measure is a sampling technic of limited accuracy which does not necessarily reflect the status of bacillary deposits in areas other than the sampled skin. However, it is not unreasonable to believe that given the same host capability, the same drug effectiveness, and the same pathogen, the remaining bacillary deposits will be eliminated in a period of time equivalent to that in which much greater bacillary deposits were actually demonstrated to be eliminated.

This concept has been introduced to patients and they have been found to accept it as rational since it relates therapy to their own performance and since most patients tend to follow avidly the results of periodic BI determinations.

Problems are immediately apparent. Obviously, if bacillary drug resistance develops, the situation becomes a new ball game. Patients may present themselves who have been previously treated elsewhere and their prior records may be unavailable. Other patients will be irresponsibly irregular in clinic attendance and in following their treatment regimen. These and other difficulties do not vitiate the

underlying principle, which is the recognition of the importance of assessing the individual host ability to dispose of the pathogen rather than focusing all attention on the pathogen's response to the therapeutic agent. In the great majority of patients it is probable that the concept will be applicable and helpful. For these it will help remove therapy from contributing to the concept that leprosy, even under therapy, is uniquely fearsome. The difficulties raised are not unusual. Attention to them falls within the realm of the art of medicine.—O. K. Skinsnes