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Drug Trials in Leprosy

some unemphasized factors

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Perusal of the voluminous literature on drug trials in leprosy is liable to produce all too often the impression that any drug has a great variability of therapeutic action: there is a disturbing imprecision and lack of uniformity of criteria. Apart from certain obvious reasons, such as small series, pairing difficulties, retrospective controls, inadequate period of observation, etc., these wide variations may be due to hitherto unemphasized causes, which will form the subject of this paper.

In drug trials, we are not only concerned with academic considerations but also with the practical problems of treatment of the individual suffering from leprosy. Fortunately at this stage we need enter into no theoretical speculations regarding the precise mode of action of the drugs employed. It is possible to investigate the effectiveness of a given drug and determine its place in therapy without having first answered the innumerable questions that plague the biochemist, the immunologist and the epidemiologist.

Although non-lepromatous leprosy is probably commoner in the world as a whole than lepromatous, it is the latter that constitutes the greatest challenge from most points of view, and for drug trials it is essential that the participating patients should be suffering from this form of leprosy. If a drug is to be effective in leprosy, its effectiveness must be conclusively shown in the lepromatous form. A drug effective in multibacillary disease may also accelerate clinical clearing of lesions in paucibacillary forms. To become a practical alternative to existing drugs, a new drug must show its superiority in no uncertain way—economic considerations quite apart. A merely marginal advantage in reducing somewhat the contagious stage of the disease, or in shortening slightly the total time of treatment necessary, or in diminishing the incidence of complications in no very definite way—this marginal advantage may admittedly indicate a limited usefulness in selected patients (for example, as a second-line drug in cases of intolerance or proved resistance), but cannot indicate that it will have a place in the treatment of a global disease affecting many millions.

In non-lepromatous disease, the varying degrees of tissue reaction to the infection—ranging from hypo-ergy to hyper-ergy—are frequently unstable and unpredictably changeable, and constitute an unknown series of variables in any trial; patients suffering from these forms are therefore best excluded from all pilot and restricted trials.

Less obvious in its bearing on therapeutic results is the kind of lepromatous leprosy and the extent and depth of the subcutaneous granuloma involved. These factors may be directly related to the duration of the infection in the individual; they are also related to the rapidity of progress of the infection and of the tissue reaction to the infection. As a result, the sheer mass of the granuloma, replete as it is with mycobacteria in globi, that must be acted upon in some way by the therapeutic agent, varies tremendously from patient to patient. Moreover, the obvious clinical appearances—macular, nodular, or infiltrative—may by no means run parallel with the amount of granuloma as revealed by histological examination. Thus, a series of trial patients may be excessively weighted in either direction, and neither careful clinical examination nor simple bacterioscopic

findings (by the slit-smear technique) nor even the histology of a few biopsy specimens (possibly atypical) may reveal the true overall picture of the extent of the tissue changes due to leprosy in the individual patient. The effectiveness of a drug may thus be masked by the mass of granuloma to be effected, and a real and marked reduction in the concentration of *M. leprae* may fail to be indicated by the bacterial index as ordinarily determined. Another aspect of the same problem concerns the concentration of bacilli in the depths of the sites smeared; the material actually examined, obtained as it is by the hazardous method of smearing, may be unrepresentative and thus give misleading impressions of the rate of decline of the index.

These considerations apply especially when results of drug therapy from Africa are compared with those from, e.g., South India, or the Philippines, where lepromatous leprosy is on the whole more severe, more resistant to therapy, more subject to reactional episodes, and more likely to be accompanied by severe eye and nerve complications. The granulomata are more succulent and florid, and the response to standard drugs as well as to newer drugs is apt to be less good than in Africa.

Degenerative changes in the bacilli indicative of non-viability may provide earlier information and more useful pointers to the effectiveness of a drug than the bacterial index; but here again, standard smearing procedures do not always produce consistent or uniform or comparable results. It may be that bacilli in different situations in the body or at different depths in the granuloma are affected to different degrees by the medication or by the complex tissue response consequent on therapy—to put it no more precisely than that. A higher proportion of bacilli from the nasal mucosa may continue to stain as solid rods than those from ear-lobes or skin.

Standard smearing techniques fail to reveal persistent foci of morphologically normal bacilli located in nerve trunks and deep organs (lymphatic glands, liver, bone marrow, etc.), which represent concealed and inapparent concentrations of viable bacilli from which reactivation of the disease may occur. Histological examination of the deep cutis may furnish suggestive evidence—in the presence of viable bacilli in the nerve fibrils—or in the endothelial cells of small blood vessels, of the existence of infection of the deeper organs, but it may not do so. Standard techniques do, however, furnish valuable information concerning the slowness of the removal of non-viable acid-fast material from the body, and there is much clinical and histological evidence concerning the immunological importance of the presence of dead matter in the tissues.

Another aspect of this problem concerns the notation employed to indicate the degree of improvement attributable presumably to the drug used. Because of its apparent precision and its arithmetical expression, the bacterial index at each site examined is accorded an importance that outweighs clinical features that are less easily represented numerically. Scales for expressing the bacterial index should be uniform from one country to another. Emphasis on the bacterial index presumes a bactericidal or bacteriostatic action of the drug investigated, which may be a fact, but which is by no means the whole explanation of its action or a precise indication of its value in limiting or reducing the complex tissue response to acid-fast foreign matter, living or dead. Thus, reduction of the generalized lepromatous infiltration may be a valuable indication of the success of chemotherapy, but this is difficult to indicate precisely by any one criterion, or by any combination of the recordable data at our disposal—clinical, histological, photographic. The human memory cannot retain accurate picture images of more than a limited number of patients under trial, say 30 or so.

Another little-appreciated factor causing variation in the therapeutic response is the phase of the leprosy process that happens to be in the ascendant when treatment is initiated. There is some spontaneous variation in the concentration of *M. leprae* in the skin and nasal mucosa, apart altogether from detectable differences between adjacent sites smeared. These variations may be at times correlated

with the waxing and waning in the apparent clinical activity, which is the obvious result of the tissue response. They may also be correlated with the proportions of degenerate forms as seen in slit-smear material examined. In general, the proportion of morphologically normal forms in untreated patients is higher in Africa than in Malaya.

The normal processes of degeneration and phagocytosis may be accelerated by factors other than the drug given. Thus, a trial may be vitiated if a disproportionate number of patients in one or other phase—progressive, or stationary, or regressing—is included; good results may be attributed to the drug in question whereas they are really due to the inherent variability of the disease. The degree of vascularisation and consequential fibrosis of a lepromatous granuloma may also have a bearing on the rapidity of the therapeutic response to a given drug. It is known that in rare cases of untreated lepromatous leprosy, all the bacilli may be degenerate in form, whereas in others all may be morphologically normal. Again, standard smearing techniques may fail to disclose bacilli in undoubtedly active lepromatous disease.

The variation in immunological response provides a parallel in non-lepromatous disease; it is known that during an acute generalized reactional phase in tuberculoid leprosy, the Mitsuda reaction may be temporarily negative—which phenomenon suggests an 'exhaustion' phase comparable with that in lepromatous leprosy, whether erythema nodosum is present or not.

It is not yet possible to do more than suggest that it is unlikely, on the analogy of other mycobacteria, that *M. leprae* should prove to be a single species, without races or strains showing biochemical and pathogenic differences. Such differences, if they are ultimately shown to exist, would go far to explain certain variations in the results of drug trials. Indeed, the possibility will open up of differentiating races or strains of *M. leprae* on the strength of different susceptibilities to chemical compounds, considered of course in relation to the other investigative procedures already in use for cultivable and inoculable mycobacteria.

The influence of hormonal and nutritional states on the course of lepromatous disease is sufficiently well recognized by leprologists engaged in drug trials. Care must be taken as a general rule to exclude children and adolescents, pregnant or lactating or menopausal females, and ill-nourished adults. The mere fact that a recently-admitted patient enjoys a better diet and regular meals, and enters upon a more sheltered life, and often attains an equable mental attitude to his disease—may all possibly have some bearing on the bacteriological and clinical course of leprosy. Such factors, operating inconsistently in small series, may vitiate a therapeutic trial if unrecognized.

The frequency and severity of reactional episodes often disturb the leprologist as well as the participating patient. It is difficult to see how these can be avoided, given the high expectation of such episodes in any series of lepromatous patients, especially the lighter-skinned, and the undoubted effect of anti-leprosy therapy in precipitating or accentuating such reactions. 'Comparable' series may not be comparable from one country to another because of the differing incidence of unpredictable reaction.

The influence of climatic factors operating during the course of a trial has often been suspected, but is difficult to prove. High temperature and high relative humidity may together coincide with the appearance or exacerbation of lepromatous lesions, just as intercurrent disease or pregnancy or parturition may apparently precipitate both leprosy and reactional episodes in lepromatous disease. Similarly, it is conceivable that seasonal variations in the immunological state of individual patients may account for some of the differences shown in one centre as compared with another.

Finally, the controversial subject of drug resistance must be mentioned briefly. Resistant forms of *M. leprae* may theoretically develop either spontaneously or as the result of therapy.

It is now possible conclusively to demonstrate such resistance. True resistance may rarely vitiate trials in small series of patients, but the not infrequent transient reappearance of morphologically normal bacilli may complicate the evaluation of a drug as well as its possible bactericidal role.

Another complicating factor is the occurrence of the different varieties of sensitivity reaction, which may affect up to 3% of patients in some African series.

To sum up, the fact that obvious and serious differences in the results of therapeutic trials do exist, is not a matter of surprise considering all the complicating factors involved; what is surprising, is that a considerable measure of agreement has been attained in different centres in widely differing circumstances.

SUMMARY

Various under-emphasized factors may complicate trials of drugs in lepromatous leprosy, and even vitiate the results. Such factors concern the extent of the lepromatous granuloma, the phase of activity of the disease process, the variability in bacillary concentration and perhaps bacillary morphology from one site to another and from different depths in the granuloma, the complexity of the tissue reaction to leprosy infection, the inherent variability of the disease, etc.

Despite these variables, a consensus of expert opinion may be reached concerning the value of a reputed bacteriocidal or bacteriostatic drug in leprosy.