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The Bases of Chemotherapy and Immunosuppressive Therapy in Leprosy

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It is a commonplace to assert that the era of rational and scientifically established chemotherapy has dawned but recently, and that the effective treatment of leprosy is embraced within our own professional life-span. In these brief years, we have progressed from the empiricism and folklore of chaulmoogra and hydnocarpus oils, and their ostensibly more respectable esters and iodized derivatives, and their salts with strong bases, through the aniline dyes and diphtheria toxoid, to the sulfones and their chemical congeners, and to clofazimine, rifampicin, etc. (2). During the same period, the experimental basis of specific chemotherapy has been firmly established, and the elegant mouse footpad investigative model has been shown to provide a reproducible framework for demonstrating the identity and viability of the causative organism, the therapeutic activity in controlled concentrations of drugs and metabolites, the occurrence of drug-resistant strains, and the initial steps in the demonstration of the precise mode and site of action of mycobacteriostatic and perhaps mycobactericidal compounds. Furthermore, during this decade, the methodology of therapeutic trials has been more precisely defined, and hence has yielded more exact, more rational, and more rapid results. The appraisal of clinical changes directly associated with active chemotherapy is now made objectively and differentiated from the extraneous phenomena with which they were in the past frequently confused.

The welcome increase in research into these and other aspects of leprosy has led to a veritable burgeoning of new knowledge and new insights. This in turn should lead to the more effective treatment of the individual leprosy patient and more efficient control measures. So far, in the world as a whole, there is little evidence that, except in isolated privileged pockets, the leprosy endemic is abating: the gaps are too large and too many between laboratory and field, and between what is known and what is applied.

In discussing the bases of modern chemotherapy in leprosy, attention will, consonant with the context of this predominantly clinical session, be largely focussed on the clinical aspects, but the increasing indebtedness to the experimental microbiologist will be tacitly assumed throughout, and is here acknowledged.

Certain bases for the assessment of chemotherapeutic activity in leprosy are now generally accepted, though different weightings are accorded to the individual findings. The investigator makes tacit assumptions that may or may not be true or relevant. He is dealing with patients who are human beings, and not experimental animals, and he is ethically responsible for the local and remote results of his acts of commission and of omission. To the conscientious clinician, leprosy is more than an infection with *M. leprae*: it is the sum of the physical results of such infection, together with the economic and psychologic consequences of social prejudices and pressures.

Clinically, management is much more than chemotherapy. And, indeed chemotherapy may be irrelevant or positively misleading if it is confined to a study of the isolated phenomenon of the presence and appearance of certain organisms rendered

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visible by staining with carbol fuchsin. These latter may represent but a stage in a complicated life-cycle, and their extreme paucity in certain lesions that are by definition leprosy should at least engender an attitude of caution.

Another *caveat* concerns the extremely vigorous tuberculoid response seen at the cellular level, the developed cell-mediated immunity. The presumably provocative biochemical antigen, as it is produced in successive centrifugal zones corresponding to slow and scanty bacillary penetration, is indirectly responsible for such obvious macroscopic pathologic changes as hyperemia, impairment of pigment formation, diminution of cutaneous sensation and disturbance of hair growth. Despite the apparent absence of viable mycobacteria, and the rarity of even acid-fast material in such lesions, mycobacteriostatic drugs seem to have distinct activity in accelerating and perhaps initiating resolution. In point of fact, some workers suggest that the long-acting sulfonamides, for instance, appear to be more active than the sulfones in this respect, more rapid in their facilitation of the repigmentation of tuberculoid lesions.

Another group of observations concerns the mode of action of the drugs used in leprosy ([3, 5]). The phenomenally low serum concentrations of dapsone that are bacteriostatic might suggest that there may be more to its action than that of a partial antimetabolite on the analogy of para-amino-benzoic acid and the sulfonamides ([4]). In fact, the pharmacodynamics of dapsone seem to open up several new vistas. For example, its value in dermatitis herpetiformis, in which it has virtually replaced the sulfonamides: it controls the condition (whose etiology is unknown), and it can be given in high doses (200-300 mgm. daily) for long periods without causing toxic signs in skin or nerves. In many kinds of mycetoma, caused by a variety of organisms, notably *Nocardia sp.*, dapsone is the drug of choice, having replaced iodides, gentian violet, nystatin, etc. In malaria, the sulfones are finding a new and important range of activity, with a specific action on *Pl. falciparum*. More recently, dapsone has been used successfully in acne, where its mode of action may lie in its biologic capacity to modify sebum secretion rather than in any hypothetical disinfectant or bactericidal action on *B. acneiformis* or the rarer *Staph. albus* (not *aureus*), secondary invader of comedones. The tetracyclines and the estrogen derivatives, long in vogue in treating severe adolescent acne conglobata, and resistant acne vulgaris, also appear to act in similar fashion. Another link with an essentially noninfective condition is provided by some collagen diseases, in which dapsone may possess properties similar to those of the corticosteroids and butazolidine. The direct antimicrobial action of dapsone, which indeed was its first action to be experimentally investigated by British and French workers over 30 years ago, is sufficiently well known to be dismissed by a mere passing reference; black marketeers in West Africa are as well aware of its use in gonorrheal infections as are orthodox practitioners of its value in ulcerations, not necessarily leprotic or trophic. There is evidence that the exhibition of dapsone in early mycosis fungoides will prevent the development of tumoral lesions. For completeness' sake, mention must be made of the use of dapsone in vasculitis, Crohn's disease, Henoch-Schönlein's purpura and ulcerative colitis.

All these observations indicate the diversity of action of the drug most commonly used in leprosy, which has furthermore shown minimal activity in related mycobacterial disease, such as tuberculosis.

Similar illustrations could be drawn from other fields, such as the sulfonamides, clofazimine, rifampicin, etc., but in the main in the much more restricted area of such mycobacterial diseases as tuberculosis, *M. ulcerans* infections, etc. Enough has perhaps been said to alert the nonclinicians to the fact that there may be far more to the chemotherapy of leprosy than a simple bacteriostatic or bactericidal action. The patient—of whom we are sometimes in danger of losing sight—is not a passive repository for the multiplication of *M. leprae* in a complex biologic tissue-culture system, but a participating, reacting and suffering individual who wants to get bet-

ter of his "leprosy." He is more interested in this than in the concentration or morphology of the *M. leprae* in his tissues.

Bearing these considerations in mind, we may briefly comment on the accepted criteria for assessing the antileprosy activity of chemotherapeutic agents:

Clinical amelioration. In such a disease as leprosy, clinical changes are notoriously difficult to assess and to quantify ([6]). They are slow, affect structures and functions in varying ways, and may bear no direct or linear correlation with the bacteriostatic or bactericidal action of the drug being given. Many earlier drug trials failed to distinguish between the essential and the derivative in, for example, changes in lesional pigmentation and in nerve size or tenderness. They grouped together primary effects on bacillary granulomata and secondary results in diminution of cellular activity in pauci-bacillary disease. Some of them confused complex antiseptic action in infected neuropathic ulcerations with progressive intraneural fibrosis consequent on antibacterial activity and inflammatory response. By confining therapeutic trials initially to patients suffering from active and progressive lepromatous or near-lepromatous leprosy, confirmed by all necessary procedures, and untreated, the direct effects and consequences of bacteriostatic or bactericidal activity can be more readily and more accurately assessed. The extreme slowness of the changes, and the absence of a definite clinical end-point are in keeping with the nature of the infection, and constitute ineradicable difficulties inherent in therapeutic trials in leprosy. In general, the theoretical advantages of pairing, placebo treatment, and double-blind assessment are minimized by practical and ethical considerations. The usual progressive worsening of patients with lepromatous leprosy, left without treatment, provides on the whole and in a sufficiently large group, a sounder scientific baseline for evaluation of the efficacy of a drug than the demonstration of slight clinical differences. The comparison is really between no treatment and the treatment being investigated. The patient provides his own control, his own baseline, even if he is assumed to be clinically static and nonprogressive. Unbiased, independent and well-qualified assessors are only rarely available, and the absence of subjective bias is difficult to achieve in evaluating unquantifiable data.

Bacteriologic changes. From 1960 onwards, we have used a simple arithmetic notation to indicate the average percentage of morphologically normal bacilli in smears taken by standard techniques from selected skin and nasal mucosal sites in patients with multibacillary forms of leprosy ([1]). This index provides a delicate and reasonably precise and comparable indication of antimycobacterial activity, and represents the resultant of bacterial multiplication, degeneration and evacuation. When evacuation is minimal, and new bacilli fail to appear, the bacteriostatic activity of the trial drug is established by the high percentage of degenerating forms, i.e. acid-fast material, of recognizably bacillary outline, that fails to stain regularly and deeply. The initial Morphological Index apparently varies from country to country independently of the criteria adopted for normality, but in the same reliable and practised hands comparable results should be obtained. Verification by utilizing the mouse footpad is a valuable method for demonstrating viability in an admittedly artificial micro-environment. The Morphological Index bears no essential relation to the initial height of the Bacterial Index or to changes in the latter. It is a matter of great interest that in Mitsuda-negative lepromatous leprosy, the Morphological Index should vary within such wide limits in the untreated patient. There may be no cell-mediated immunity, but the life-span of individual bacilli may apparently vary enormously from patient to patient, and the Morphological Index (in extreme cases, admittedly) may be 0 or 100 per cent in genuinely untreated patients. This observation should make for extreme caution both in the selection of patients for inclusion in drug trials and in the interpretation of the results.

Other factors, such as the discontinuity of the bacilliferous granuloma and the persist-

ence of pockets of morphologically normal bacilli, may also complicate—if not partially vitiate—the results.

The reappearance of foci of normal bacilli, aggregated into well-defined mushroom-like areas, and sometimes in visible papules, may or may not herald bacteriologic relapse, caused by the proliferation of bacilli which may or may not be drug-resistant.

Histologic examination of material from the active edges of lesions provides not only invaluable confirmation of the classification, but also data concerning the presence, disposition and morphology of the bacilli and the changes in both bacilli and cellular infiltration that accompany successful therapy. The histopathology of the broad intermediate zone between near-tuberculoid and near-lepromatous leprosy provides perhaps the most intriguing and the most puzzling features, with increase in cellular response with treatment (reversal reaction), and decrease in resistance on each successive episode of exacerbation. Histologic examination, while undoubtedly superior to the slit-smear technique in many respects, remains a research tool rather than a procedure for routine use in mass leprosy control schemes. It supplements and corrects any conclusions based on the examination of a minute and perhaps atypical area of dermal tissue. Long experience engenders a very healthy respect for the capacity of *M. leprae* to persist for years in the tissues without revealing its presence clinically.

The immunologic findings are of minimal value in the diagnosis of leprosy and the evaluation of the results of treatment, though they may be of fundamental importance in pathogenesis and classification, and hence in prognosis. In early leprosy (indeterminate or minor tuberculoid), and in children, the degree of positivity of the lepromin reaction may not correspond with the clinical findings, and in major tuberculoid leprosy passing through an acute inflammatory phase, the lepromin reaction may be transiently negative—an example of immunologic exhaustion.

There is growing evidence that the slight immunity present in persons developing lepromatous leprosy is somehow reduced still further by the actual infection, just as the potential reactivity of persons developing tuberculoid leprosy is somehow enhanced as cell-mediated immunity increases.

Notwithstanding the range of inherited ability to lyse *M. leprae*, the individual differences in metabolizing and utilizing antileprosy drugs, and the broad racial differences in susceptibility and disease-patterns, the bases of chemotherapy are generally well established. I leave to the biochemists the detailed discussion of the mechanism of drug action, and the importance of such structures as lysosomes in the dissolution of the organisms. The most important aspect of applied chemotherapy yet virtually untouched is the removal of effete antigenic acid-fast material from the body of the patient cured of his infection but still suffering from "leprosy."

The bases of immunosuppressive therapy in leprosy are only now becoming less imprecise and more rational than has been the case hitherto ([6]). The number of drugs suggested for the treatment of acute reaction in leprosy, and the contradictions in the literature, are in the main due to:

1. Lack of definition of the clinical states considered.
2. Collection of diverse syndromes into a spurious unity.
3. Variations in the seriousness of reactional episodes not only between one type of leprosy and another, but also between examples of apparently the same type within a country, and also from different countries.
4. Great diversity of clinical phenomena associated with essential unpredictability.
5. Absence of objective, measurable criteria for registering in comparable fashion any improvement attributable to chemotherapy.

Successive meetings of experts attempting to correlate and synthesize diverse pronouncements have been less successful in adumbrating the bases for immunosuppressive therapy in leprosy than individuals and groups that have studied the matters intensively. The reasons for the confusion,

itemized above, are now yielding to critical examination, and the emergence of agreed bases is at least becoming a reasonable possibility.

1. **Lack of definition.** The hotchpotch of inflammation and tissue sensitivity on the one hand, and the specific response of target organs (such as the uveal tract, the peripheral nerves, etc.) on the other, should now be resolved into more precise categories, as the findings of histology and immunofluorescent investigations are becoming available.

2. **Variations in gravity.** The extreme range of seriousness of acute episodes, from a few transient superficial skin lesions to an inexorably progressive generalized systemic condition, makes for noncomparability of results of therapy unless strict criteria are observed. Thus, the condition should be established and severe, showing no spontaneous amelioration or violent exacerbation, and permitting gradation into categories. Generalizations based on observations in one country and dealing with clinical states typical of one or a few racial types, are not necessarily applicable to another situation. Caucasians and Chinese seem to be subject to more severe, more prolonged and more unpredictably violent episodes of reaction than the deeply-pigmented Bantu. Similarly, minute doses of dapsone may precipitate a return of severe signs and symptoms in certain types of patient though not in others.

3. **Diversity of phenomena.** While the signs of systemic involvement usually run *pari passu,* and severe edematous and erythematous infiltration may be the visible evidence of a widespread tissue sensitivity, one organ may be involved much more than others, e.g., the skin, the uveal tract, the Leydig cells of the testis, the peripheral nerves. If any one criterion is utilized to the exclusion of others, spurious impressions of comparability may be presented.

4. **Measurable criteria.** Anti-inflammatory activity may now be objectively demonstrated by the cotton pellet and the carrageenin tests, and the presence of fluorescent antibody may be shown by special methods. Body temperature, pulse rate, leucocytosis, proteinuria, are more amenable to objective measurement than malaise or pain, or even the redness and elevation of skin lesions. The value of serial histologic examination is limited: the picture varies so greatly in cellular density, in cell type, in degree of endarteritis and hyaline medial degeneration, in the density and morphology of *M. leprae,* that improvement under treatment is difficult to assess on these grounds alone.

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The chemotherapeutic rationale of drugs commonly used for the control of the serious forms of acute exacerbation in leprosy is far from being precisely understood. We are still at the stage of empiricism and pragmatism. There is still disagreement concerning the advisability of suppressing or continuing antileprosy treatment during severe reaction, some holding that the clinical state is unaffected, while others point to the observed precipitation of new lesions on every exhibition of even minute amounts of an antileprosy drug. There is also disagreement concerning the reactogenic properties of drugs, singly or in combination.

Apart from the sedatives, of the drugs in use 20 years ago (methylene blue, mercurochrome, acriflavine and the rest) only the *antimonials* seem to have survived; and their efficacity—given intravenously as sodium antimony tartrate or intramuscularly as a proprietary preparation—seems well attested. Loosely termed "anti-inflammatory" drugs, they are prescribed on empirical grounds.

Chloroquine is virtually the only antimalarial in general use for this purpose. Its action is curiously selective, appearing either to act decisively in the individual on every occasion, or not to act at all. The complex mode of action of this drug is to be seen in relation to its use in such diverse conditions as malaria, rheumatoid arthritis, lupus erythematosus, etc.

The **corticosteroids,** as anti-inflammatory drugs, have an assured place in the control of the reactive state. Usually given orally and parenterally for their systemic effects,

they also have a demonstrable efficacity when infiltrated locally (perhaps with hyaluronidase) into acutely edematous peripheral nerves, or introduced subconjunctivally in the case of acute iridocyclitis. Even when antileprosy treatment is temporarily suppressed during the administration of corticosteroids, multibacillary disease does not appear to worsen as rapidly as it might.

Clofazimine has an experimentally established anti-inflammatory action; it must be given in doses adequate to the gravity of the reaction. In this respect it is no different from the corticosteroids. A useful property of this drug is that it has a mycobacteriostatic action in addition. The exact mechanism by which it controls the clinical manifestations of acute reaction is unknown, but is probably unrelated to its concentration in cells of the reticuloendothelial system. Clofazimine is thus valuable in established serious exacerbation, in reaction-prone patients with lepromatous leprosy, and in dapsone-resistant leprosy.

Thalidomide has a consistent and rapid efficacy in controlling the acute reaction in lepromatous leprosy, and were it not for its neurotoxic and teratogenic side-effects, it would doubtless enjoy a more widespread vogue. Its sedative action (like that of chlorpromazine) may account for a small part of its effect in leprosy, but the mechanism of its apparently specific action is as yet unexplained. Certain breakdown metabolic products and related cyclic imines may have a similar anti-inflammatory action.

Flufenamic acid, Tanderil (oxyphenbutazone) and indomethacin and other anti-inflammatory agents have been used in leprosy, but in small series or with equivocal results.

The immunosuppressive drugs, cyclophosphamide, amethopterin and 6-mercaptopurine, given experimentally to mice infected with *M. marinum*, apparently stimulated bacterial growth; mice infected with *M. tuberculosis* died sooner than normal when given these drugs. In experimental *M. leprae* infections, there was apparently no promotion of bacterial growth, but the doses of cyclophosphamide had to be reduced because of drug-associated mortality. In human beings suffering from leprosy, cyclophosphamide does not control acute lepra reaction or improve the clinical condition of patients suffering from erythema nodosum leprosum.

Cytostatic or cytotoxic agents such as Natulan, Ancyte and Vercyte have no apparent efficacity when given to patients in the throes of lepra reaction.

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This brief résumé of drugs used to control the manifestations of acute reaction indicates the complexity of the clinical condition rather than the precise biochemical bases for the beneficial results observed.

SUMMARY

Within our professional life-span, the chemotherapy of leprosy infection has progressed from irrational folklore to precisely-tailored chemical synthesis, from haphazard polypharmacy and clinical impressions to purposeful therapy and objective appraisal. Of the twin bases of modern chemotherapy—experimental and clinical—only the second will concern us in this predominantly clinical session, but the clinician's debt to the experimental biologist will be apparent throughout.

1. Clinical amelioration. Earlier trials failed to distinguish clearly between essential and derivative, primary and secondary, bacilliferous granuloma and residual cicatrization. By confining therapeutic trials initially to patients with lepromatous or near-lepromatous leprosy, the direct effects and consequences of bacteriostatic or bactericidal activity can be more readily and more accurately assessed, and the complex tissue response to living and dead mycobacteria can be nullified.

2. Bacteriologic changes. From 1960 onward, we have systematically employed an arithmetical notation to indicate the percentage of morphologically normal organisms present in the multiple sites regularly smeared. This notation provides a delicate and precise indication of antimycobacterial activity, and is largely independent of the

changes in the level of bacterial concentration in the tissues. Pockets of viable bacilli may persist in certain situations, to multiply temporarily. Drug-resistance may be associated with intermittency of low-dose treatment.

3. Histologic examination provides evidence for confirmation of classification, of gradual changes in immunologic pattern, of persistence of viable bacilli and their precise location, and the phenomenal resilience of *M. leprae* confronted with mycobacteriostatic drugs and tissue inhibitory factors.

4. The immunologic state, as indicated by the lepromin reaction, furnishes data of subservient value especially in the intermediate (or borderline) group.

The bases of immunosuppressive therapy in leprosy are rather more difficult to define and delimit, since the criteria for control are less precise, and the clinical states are complex and possibly multifactorial in origin.

The first desideratum is comparability—of etiology (if possible), of severity, and of prognosis. The range of meaning of the terms "reactions" and "exacerbation" as used by clinicians and as seen in the literature indicates the need for agreed uniformity of nomenclature. Other desiderata are: objective criteria for therapeutic efficacy; exclusion of the normal range of variability in clinical progress; precisely assessable changes attributable to medication; scientific appraisal of the treatment instituted in the context of ethical obligations to the sick individual.

The present position of anti-inflammatory drugs used in leprosy, (chloroquine, corticosteroids, clofazimine, thalidomide, flufenamic acid, indomethacin) will be briefly reviewed in the light of these considerations.

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