Editorial

BORSTEL 1974—THE CHEMOTHERAPY OF LEPROSY TODAY AND TOMORROW

Of the making of congresses—and colloquia and symposia—there seems to be no end, and much attendance is a weariness to the flesh and the spirit. Will Borstel 1974 pass into history as "just another colloquium", or will it be regarded as a landmark, recognizable, important and significant? Who can say, now?

Borstel was purposely different, in several ways. All the participants were chosen and invited because of their interest in the drug treatment of those afflicted by leprosy, and because of their special expertise in some aspect of chemotherapy. The area of discourse was more or less strictly delimited, though it should surprise no-one that the wide-ranging papers and discussions touched upon, and profited from, a multiplicity of scientific investigations. Personal experiences along the growing frontiers of knowledge were at a premium, and time was not wasted in any tedious rehashing of the accepted and the obvious; during the full day devoted to discussion, the incisive questioning of inadequately supported assumptions by experts recently attracted to leprosy, was time and again evident.

No conclusions or recommendations are forthcoming, and no weighty (or frothy) pronunciamentos. And no feeble mice, either, will be seen creeping from some noisy mountainous eruption. "Borstel 1974" was useful, very useful, and important. Its importance will become apparent in a more critical attitude among the individual participants, and a greater keenness—from strictly scientific or avowedly humanitarian motives, or both—to discover how best to treat the patient who suffers from this fascinating and challenging mycobacterial infection.

As "Borstel 1974" recedes into the middle distance and its impact becomes somewhat diffused, some of its emphases may be selected for brief comment. These emphases were mostly brought out by sharp differences in approach and experience between participants—a sure indication of incomplete knowledge and the need for more research.

Take the "simple" concept of the Morphological Index. To some, the MI is the most delicate and valuable pointer to the efficacity of a drug regimen. To others, it may provide transient and misleading evidence of an inimical microenvironment. To all, it is a temperamental criterion, rather too sensitive to slight differences in the techniques of processing, fixing and staining, to temperature, to concentration of reagents. It is not only the morphology, the general appearance, of individual organisms that may vary within wide limits depending on the technique employed, but the concentration of optically visible bacilli in smears and histological sections. If such serious discrepancies are disclosed in the best

laboratories, the implications for drug trial evaluations and for field projects must be critically reviewed.

A related theme on which rather more unanimity prevailed, was the urgent need for more centres of excellence, where trials of new drugs could be undertaken in first-class conditions. Ideally, such centres should be linked with areas of high leprosy prevalence, and be able to draw upon adequate numbers of co-operative patients with untreated lepromatous leprosy as well as upon independent and experienced clinical assessors. Although this ideal may enshrine the mutually incompatible, it is well worth restating.

The difficulties and pitfalls inherent in trials of single drugs and of more than one drug given concurrently were brought out vividly in papers and discussions. The right questions cannot be answered if the wrong patients are chosen to participate in the trials. The presence of some degree of cellular immunity in patients with subpolar lepromatous leprosy may vitiate the conclusions drawn concerning the mycobactericidal or mycobacteriostatic activity of the drug being investigated. And tissue clearance is quite unrelated to such activity. Perfectly matched controls are hard to come by in leprosy, a disease in which sex and age and classification may be more readily measurable than comparable degrees of tissue response in this variable host-parasite relation. When combined therapy is under consideration, the clinical and bacteriological advantages conferred by "the other drugs" should be more than marginal over the improvement observed when the most active drug is given alone. Multi-centre trials may add no substantial positive element, and by reason of variable criteria may actually detract from tentative conclusions derived from a single-centre trial thoroughly well conceived and executed. In the nature of things, the objectives of giving combined therapy in leprosy are difficult to evaluate: the chimeras of reduction in the period of infectivity, of rapid tissue clearance and of prevention of nerve damage having been dispelled, there remains the awkward question of the postponement of the emergence of resistant strains of *Myco. leprae*. On theoretical grounds, combined therapy may be mandatory, but convincing evidence is not yet forthcoming in leprosy, and in any case, the practical difficulties in most countries appear at present to be insurmountable.

The sombre threat of drug-resistance emerging whenever leprosy treatment had been available for more than a decade, brought an air of sober realism to the Colloquium, and reminded the participants not only of the quasi-unique nature of the bacillus-host commensal relation in leprosy, but also the need for continued treatment after apparent arrest and for the investigation of novel methods of treatment. The possibilities of immunotherapy (being outside the immediate purpose of the Colloquium) were but lightly touched upon, but tentative advances in the direction of stimulating lymphocytes by biological means (such as Transfer Factor) or by drugs (e.g., Ducton, Thymosine) will doubtless engage the future attention of many forward-looking researchers. The possibility of a modification of cellular activity cannot be ruled out: cell-mediated immunity needs to be induced somehow in patients suffering from lepromatous leprosy, and depressed in those suffering from tuberculoid leprosy and in danger of incurring damage to peripheral nerve trunks. But the continuing problem of instigating or accelerating tissue clearance of effete mycobacteria, while recognized at the Colloquium, received no answer.

Another area of concern and uncertainty proved to be the whole question of definitive arrest of multibacillary leprosy, of "cure" in the old simplicist sense.

Hopes had been rekindled that rifampicin would be a *therapia sterilisans magna,* but the invulnerability to this drug of dormant leprosy bacilli, particularly in the bone marrow, and the presence of persistors in diverse tissues (perhaps particularly in nerve and muscle) served to dampen the earlier optimism. The curious immunological consequences of intermittent rifampicin therapy provided a salutary conterbalancing argument against the attractive suggestion that the drug might be used in high doses at long intervals as treatment and prophylaxis.

For practical purposes, however, the patient with arrested lepromatous disease may not only be regarded as non-contagious; his disease is arrested—he is apparently cured. "Cure" is essentially a clinical term, with sociological overtones and implications; it does not connote the destruction and disappearance of the last living leprosy bacillus in the recesses of the bone-marrow or elsewhere. As pathologists, we may not like the term. As field workers we may wish to retain it. As clinicians with some pathological knowledge, we recommend our patients to continue with treatment and we observe them as conscientiously as we can, clinically and bacterioscopically, for as long as we reasonably can.

Once again, the field worker has to do the best he can, given the intractable realities of finance and staff shortages and public opinion. He must compromise in order to achieve the greatest good for the greatest number, and not to prejudice the whole leprosy programme by insisting on unattainable ideals. The present predicament is by no means hopeless, of course, and the discovery of the mycobactericidal properties of rifampicin suggest that an even more effective antibiotic may yet be found that would change the outlook for the individual patient and the community at risk.

It would be unrealistic to suggest that the Colloquium witnessed any dramatic disclosures of new therapies or new insights into the treatment of leprosy, but it would be true to conclude that the accumulation of new knowledge, particularly in the realms of microbiology and immunology in regard to leprosy, makes for sober, solid realism as all concerned prepare themselves more adequately for the next leap forward, *"reculer pour mieux sauter"*.

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