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Editorial

LEPROSY REVIEW. This issue of *Leprosy Review* marks the close of an era. Volume 40—not XL, you notice—will make its debut early next year with the publication of No. 1. The familiar colour of the cover will be retained, but the style of printing will be modernised and, we hope, more attractive. There will be minor changes that the discerning eye will notice and approve.

Leprosy Review will, as heretofore, be published four times a year, as early in each quarter as the preparation of copy for the press will permit.

This will not be the first time that this quarterly publication of the British Leprosy Relief Association has taken on a new look, but this time the new look will coincide with new publishers. While LEPRA will continue, through its Medical Committee, to be responsible for the content and policy of the journal, the burdens and risks of publishing will henceforth devolve upon an established and experienced publishing house, The Academic Press Inc. (London) Ltd., whose address is:

BERKELEY SQUARE HOUSE,
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Articles intended for publication should be submitted to the Chairman of the Editorial Board:

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Instructions to authors will appear in each subsequent issue of *Leprosy Review*, as well as information regarding reprints.

While the resources of our new publishers will be mobilised in favour of the promotion of *Leprosy Review* and its introduction into places where it should be read, in the last resort the appeal of such a publication depends on the quality and worth of its contents. Therefore, the Editorial Board will welcome and critically consider any good original work on any aspect of leprosy.

The annual subscription to *Leprosy Review* has unfortunately had to be raised to £3 per annum to meet greatly increased costs. The Editorial Board will endeavour to keep the price at its present level and give the greatest possible value for money.

THE NINTH INTERNATIONAL LEPROSY CONGRESS. REFLECTIONS ON LONDON, 1968. In the eyes of many, 'London 1968' will go down in history as the Congress at which the science of leprosy emerged to take its place among the other major diseases long since admitted to the academic pantheon. More work, more good work and more good original work was reported at this Congress than at any of the previous eight. And this work came not only from those who have devoted themselves for years exclusively to the problems of leprosy, but also from investigators who have entered the leprosy field from other and related branches of medicine. Newcomers with well-stocked minds and well-polished investigative tools and techniques have been bringing their expertise to bear on the unsolved mysteries of the slightly contagious mycobacteriosis that remains the last of the major transmissible endemics to yield its secrets.

Of course, there were some papers read (in full or by title) that may have contributed little or nothing new, but they did provide evidence of the authors' application and industry. Other papers took a new look at old problems with refreshing iconoclastic zeal. The segregated leprologists of a bygone era must now rub shoulders with their fellow scientists, speaking the same language and adopting the same objective criteria for their investigations and conclusions. This is all to the good. The more exchange of ideas and skills, the more critical appraisal of reported work, the better. Of course, we have our own special problems in leprosy, and our own special ways of looking at them. But the mystique, the aura of uniqueness that

has been perhaps unwittingly built up over the years, must go before the piercing, penetrating light of detached scientific investigation. The confused and confusing literature on leprosy has been almost a byword among our fellows. If you look long enough in the journals, you can find evidence for almost any answer to almost any question on any aspect of leprosy. Contradictory and contrary views have been current on any major facet of leprosy you like to name. But, Sir Max Rosenheim reminded those who listened enraptured to his speech at the closing Banquet at the Savoy, so august a body as the Royal College of Physicians (London) reported in 1867 that the 'all but unanimous conviction of the most experienced observers' was 'quite opposed to the belief that leprosy is contagious'. Yet, within 30 or 40 years, one country after another was feverishly enacting laws for the compulsory segregation of people who suffered from the highly contagious disease called leprosy.

It is the same with treatment. Periods of naïve optimism have been followed by epochs of the most abject despair. Chaulmoogra oil was wonderful, a tremendous advance . . . and then, practically worthless. Any and every conceivable drug is effective in acute exacerbation . . . and the same proportion of patients gets better whatever the medication given. There must be more self-criticism and more open-minded welcoming of the criticism of others if consistent progress in therapy, unpunctuated by preventible over-enthusiasms and by avoidable and unwarrantable pessimisms, is to be registered in the future.

The Congress emphasised again and again the great steps forward that have been taken since Rio de Janeiro, 1963, and Tokyo, 1958. The experimental model of limited multiplication of *M. leprae* in the mouse footpad is now supplemented by the widespread dissemination of the organism in the thymectomized and irradiated mouse. Further studies in immunology are presaged by the reports on cell-mediated resistance and the use of anti-lymphocytic serum. The building-up of new knowledge in these spheres, the continuing interchange of ideas and sophisticated techniques, and the cross-fertilisation of active minds already make Bergen, 1973, an exciting prospect.

The Minister of Health in his speech inaugurating the Congress, referred to the need to resolve the question of BCG prophylaxis in leprosy, a problem bedevilled by conflicting data for the past thirty years. Practically speaking, this may be the most urgent of our tasks, for control schemes are not only both costly and protracted, but they appear as yet to have made little general impression on the world prevalence of leprosy.

The Minister also referred to the need for co-operation between all concerned with leprosy: the scientist and the field-worker; the voluntary agency and the official national and international bodies; the medical profession and its invaluable and indispensable counterparts. The Secretary-General of the Congress sounded the same note in his address on 'The Way Ahead: blue-prints and guidelines' in the Session on Co-operation and Priorities, as well as in his summing-up at the Closing Ceremony of the highlights of the week's work.

We shall publish in the pages of *Leprosy Review* some of the papers presented at the Congress, and meantime repeat the hope expressed more than once that there should be some kind of continuing organisation to keep in close touch those who were brought together for an all-too-brief week in London, 1968.

MEN AND EVENTS

Dr. Ernest Muir, not quite so agile as he was but still very alert, was present at two sessions of the Congress. He was given the ovation he so richly deserves.

Dr. Robert Cochrane, on relinquishing the position of President of the International Leprosy Association—a position he has held since the lamented death of Dr. J. M. M. Fernandez—was accorded the title of President Emeritus. He will be working at the Shinyanga Leprosarium, Tanzania, with his wife, Mrs. (Dr.) Jeanie S. Cochrane.

Editor of the International Journal of Leprosy. In greeting our sister journal, we express our deep admiration for the magnificent work of

the retiring Editor, Dr. Esmond Long, and extend a warm welcome to the incoming occupant of the editorial chair, Dr. Olaf K. Skinsnes, Professor of Pathology in the University of Honolulu, Hawaii.

Monsieur Raoul Follereau, founder of World Leprosy Day and of The Order of Charity, paid a brief visit to London for the Congress. At the Session on 'Co-operation and Priorities', he made a characteristically impassioned plea that the individual leprosy sufferer must everywhere be accorded his full social and legal rights.

Dr. Frans Hemerijckx, well-known for his part in organising a model leprosy control service in the Province of Katanga in the old Belgian Congo, and then for his leadership in the Belgian Leprosy Control Centre at Polambakkam, South India, and his advisory activities throughout India, received the Damien-Dutton Award for 1968 at the hands of the founder and present Director of the Damien-Dutton Society (Mr. Howard E. Crouch) during the Closing Ceremony of the Congress. The Award was first made in 1953, and Stanley Stein (the Editor of 'The Star', Carville) was the recipient. Two of those honoured in earlier years. Mrs. Eunice Weaver (Brazil) and Dr. Robert G. Cochrane (India and England), were present.

The Award was established to honour those who have made some outstanding contribution towards the conquest of leprosy, through medical care, research, rehabilitation, education, philanthropy, etc. The handsome and weighty mounted bronze plaque bears the effigies of Father Damien of Molakai and of Brother (Joseph) Dutton, who spent 44 years working both with Father Damien and after the latter's death.

Bergen, 1973. The next (Tenth) International Leprosy Congress will be held in Bergen, Norway, from Monday, 20 August, onwards. Negotiations extending over several months culminated in the transmission by the Norwegian Government of an official invitation to hold the next Congress in Bergen. The invitation was enthusiastically and gratefully accepted by the General Meeting of Members of the International Leprosy Association held during the recent (London) Congress. Bergen, 1973, will coincide with fitting celebrations to mark the centenary of Hansen's outstanding work on elucidating the causative organism of leprosy, *Mycobacterium leprae*.

A.L.E.R.T. and ELEP. Profiting from the presence at the Congress of personalities associated with A.L.E.R.T. (the All-Africa Leprosy Rehabilitation and Training Centre, Addis Ababa) and ELEP (the Association of of European Leprosy Organisations), meetings of the Medical Consultative Committees of these two bodies were held, at which matters of medical interest and policy were discussed.

I.S.R.D. The World Leprosy Committee of the International Society for Rehabilitation of the Disabled, under the Chairmanship of Dr. Paul Brand, held a meeting during the Congress. Since leprosy is one of the world's greatest crippling diseases—if not the greatest—it is most fitting that the Leprosy Committee should make its voice heard in the places where policy is determined and decisions made.

The next World Congress of the I.S.R.D. is to be held in Dublin, September 14-19, 1969. Leprosy will again figure—and that more prominently than at previous Congresses—on the programme.

The *Association de Léprologues de Langue Française* held an informal meeting during the Congress. We welcome the *Bulletin* of the Association, very well produced and excellently printed, which contains the papers presented at the Colloquium held in Tunis, at which the *Association* was founded. (Secretary-General: Dr. A. Basset, Clinique Dermatologique de la Faculté de Médecine de Strasbourg, 1 Place de l'Hôpital, 67 Strasbourg, France.)

Obituary. Dr. H. W. Wade, 1886-1968. One by one, the giants of the past slip away from us. The pioneers of leprosy research and treatment may go, but their influence abides and their example continues to inspire and stimulate.

Herbert Windsor Wade was such a one. Nobody has had a more far-reaching and seminal effect on the understanding of the

pathology of leprosy than he. Trained as a tissue pathologist, and serving in turn as demonstrator in histology and pathology before he graduated in medicine, Wade will always be remembered for his critical observations and most painstaking research. Most of his work was done in the Philippines at Culion, where he pursued his elegant investigations and hammered out his masterly Editorials for the *International Journal of Leprosy*.

He popularised the 'scraped-incision' method for ascertaining the mycobacterial content of dermis and nasal mucosa; he made precise observations and descriptions of tuberculoid and borderline leprosy; his work on immunology in leprosy, on the preparation of lepromin and the significance of the lepromin reaction, is well known and universally recognised.

He was unsparing of himself and looked for the same high levels of critical evaluation in others. For clarity and precision of thought and expression, he has been rarely equalled in the world of leprosy, and never excelled. He could give the impression of being abrupt and unsympathetic to those who failed to reach the exacting standards he demanded of himself, but to those who knew him better this mask concealed an incisive and alert mind that was for ever probing for truth.

As another mark of his greatness, we may recall the many distinguished research workers who have been inspired by his example as they have worked alongside him in the laboratory.

'Prexy' Wade was accorded many honours. He was Chairman of the Leonard Wood Memorial Conference on Leprosy held in Manila in 1931, at which the International Leprosy Association was formed. He was the first Editor of the *International Journal of Leprosy*, relinquishing the task in 1963. Elected President of the Association in 1946—the third to hold the office—he became Emeritus President in 1963 on retiring from active work at Culion.

As a young doctor trying to tackle a huge leprosy problem in the Belgian Congo, I admired 'Prexy' Wade from afar, scarcely daring to correspond with him, but eagerly reading his early Editorials and articles. Later, I appreciated his helpfulness and encouragement when I first ventured into print on leprosy. His masterly grasp and clear exposition of the great puzzles of leprosy pathology and the minutiae of histopathology delighted and sometimes amazed us as we sat at his feet. My last personal contacts with him were enlivened by a discussion on the lysosome and its possible role in leprosy.

We salute him, and honour his memory.

S. G. Browne.

The Ninth International Leprosy Congress

Report on the Week

Many readers of *Leprosy Review* were among the registered participants or day visitors at the Congress. For those who were not privileged to be present, the following report may provide at second-hand an indication of its importance and significance. When close on 500 people interested in leprosy converge from over 70 countries to one centre, and there listen to 235 papers delivered in 4 languages in 17 working sessions, no-one can predict the immediate and remote results.

Her Majesty Queen Elizabeth II, whose personal interest in leprosy is well known, sent a special message to the Congress, of which she graciously consented to be Patron. The Vice-Patrons represented diverse official, professional, local and international bodies concerned in some way with leprosy, together with the two main voluntary agencies in Britain.

Dr. Robert G. Cochrane, President of the International Leprosy Association, was President of the Congress. The Organising Committee consisted of Drs. S. G. Browne, R. J. W. Rees, D. S. Ridley and (until his untimely decease) J. Ross Innes.

WORKING PARTIES

Working parties were held both before and after the Congress. Some were organised by the World Health Organization (on the standardisation of lepromin; *M. leprae;* leprosy therapy; methodology in drug trials in leprosy), by the Leonard Wood Memorial (on cultivation of *M. leprae*), by Messrs. G. R. Geigy (B663 (Lampren) in the treatment of leprosy and leprosy reaction), and by the Congress (on classification; and thalidomide therapy in leprosy reactions).

SCIENTIFIC PROGRAMME

All meetings were held in the fine new buildings of the Mechanical Engineering Department of the Imperial College of Science and Technology, South Kensington, by kind permission of the Principal, Professor E. B. Chain.

Simultaneous translation was provided for all the main scientific sessions in English, French, Portuguese and Spanish. In addition, facilities were offered for translation into and from Japanese.

In accordance with modern practice in Congresses sponsored by scientific organisations, the sessions were in the nature of a series of symposia at which specific matters were considered. The Panels, which were a feature of former Congresses, found no place in London, 1968. Consequently, key leprosy workers had time and opportunity to attend the sessions, and play their full part in discussions, without being diverted by the claims of panel discussions and the compilation of voluminous reports that had to meet an inexorable deadline.

EXHIBITION

Microbiological research, osteological material from medieval churchyards in Denmark, sophisticated microscopes, leprosy periodicals, voluntary agencies—all had their activities displayed in the Exhibition Hall.

SOCIAL PROGRAMME

A very full social programme had been organised, with the express object of providing participants and their wives with opportunity for meeting and discussing.

In addition to the Welcoming Reception sponsored by the International Leprosy Association, Receptions were offered by the National Fund for Research into Crippling Diseases (at Apothecaries' Hall), by Sir Cyril and Lady Black (at the House of Commons), by The Leprosy Mission, the Ministers of Health and Overseas Development (at Lancaster House), and by the Greater London Council.

The Congress Banquet was held at the Savoy

Hotel, at which the special guest, Sir Max Rosenheim (President of the Royal College of Physicians of London), gave a most fascinating speech.

The Ladies' Committee, under the Chairmanship of Mrs. Stanley Browne, had organised a full programme of visits to places of interest for Associate Members of the Congress—to Luton Hoo, around the City of London, to Windsor, and by boat to Greenwich. For the most part, the weather was kind, notwithstanding the cloudbursts and floodings that immediately preceded the week of the Congress.

The Congress was officially inaugurated on Monday, 16 September, by the Rt. Hon. Kenneth Robinson, M.P., Minister of Health, whose speech set the tone for the week's activities. The Minister welcomed the participants, and assured them of the interest that would be taken by the Government in their deliberations. He referred to the valuable contributions made by British voluntary organisations and British scientists to the continuing fight against leprosy, and mentioned that Great Britain today had its own leprosy problem, by no means negligible. He called for more co-operation in leprosy research; he looked to the medical scientists to make some definite pronouncement on the value of BCG vaccination in preventing leprosy; and he called on all present 'never to neglect the intimate and real social and psychological problems of the sufferer and his family'. He continued, 'In your very commendable scientific investigations, you will never, I am confident, allow your interest in the cellular reaction in the mouse to cloud your concern for the human plight of the man.'

A message was read from Her Majesty the Queen, and greetings and good wishes were voiced by Alderman Sir Harold Gillett on behalf of the Lord Mayor of London and the City Corporation; Dr. L. M. Bechelli, for Dr. M. G. Candau, Director General of the World Health Organization; Mr. H. C. Edwards, Vice-President of the Royal College of Surgeons of England; Dr. S. G. Browne, on behalf of Sir Max Rosenheim, President of the Royal College of Physicians of London; Dr. B. B. Waddy, for the President of the Royal Society of Tropical Medicine and Hygiene. The Parliamentary Secretary to the Minister of Overseas Development (Mr. A. E. Oram, M.P.), and the Vice-Chairman of the Greater London Council (Mr. G. W. Aplin) were unfortunately prevented by flooded roads from attending, but managed to telephone messages of greeting.

Some Highlights of the Week's Work

The following report is taken, with the Editor's permission, from the special Congress supplement of the *International Journal of Leprosy* (Vol. **36**, No. 4). This permission is gratefully acknowledged.

In this review, I select from the Chairman's Reports of each of the scientific sessions some of the features that they themselves would wish to emphasise.

First, SESSION II: Epidemiology, including Genetics (Chairman: DR. CARL TAYLOR).

The dominant features of the epidemiology of leprosy are a general dissatisfaction with traditional approaches and a hunt for new methods. The search for genetic markers having an association with specific types of leprosy has so far furnished only suggestive leads, and no clear indication of their significance. Other methods of genetic study as are now available give as yet no indication of their potential value.

The epidemiological significance of the lepromin test continues to be minimal, and the evidence that large proportions of positive conversions are unrelated to leprosy infection, but possibly associated with non-pathological mycobacterial infections, has been increasingly demonstrated. The Karimui research project team has proved the value of intensive and continuing observations on population groups sufficiently small, and sufficiently isolated, to give consistent data; incidentally, more evidence of spontaneous healing, self-regressing leprosy lesions has come to light. More such clinical and field studies are needed.

We have been reminded of the value of anthropological research in leprosy. It may be that such factors as marriage patterns will provide suggestive leads concerning infection, and emphasise the importance of repeated close or skin-to-skin contacts with index cases disseminating viable mycobacteria from skin and nasal mucosa.

A timely reminder came from Bengal, that many healthy people not in contact with open leprosy patients, may harbour mycobacteria in skin and deeper tissues. So far, there is no laboratory confirmation that these organisms are indeed *Mycobacterium leprae*. This work underlines our lack of appropriate cultural media, perhaps including some specific adjuvants as postulated by Hanks, that will permit the cultivation and identification of *M. leprae* amongst all mycobacterial contaminants of the skin surface, and the deeper tissues. Japanese workers have demonstrated that acid-fast bacilli are found in normal human skin in subjects having no possible contact with leprosy. More intensive investigation and carefully planned surveys, with well-documented records and adequate statistical control, must be organised in an attempt to answer the simple, but extremely profound, questions. How is leprosy spread? Is there an extra-human reservoir? Where does *M. leprae* live? And how does this fastidious organism, with its extremely particularised growth requirements, manage to survive and to multiply? These are questions that still await elucidation. The simple questions, the most profound, are frequently the most difficult to answer.

Dr. C. C. Shepard's Session (IV) was one of the most important of the Congress. More new work, and more new significant work was reported here than elsewhere. Details of accurate technical estimations of limited multiplication of *M. leprae* in the mouse foot-pad, were supplemented by Rees' work on the production of widespread bacilliferous granulomata in the thymectomized and irradiated mouse.

The observation that muscle as well as nerve tissue provides a suitable nidus for mycobacterial multiplication has been further investigated by several workers.

The fundamental immunological differences in the human host, differences that are clinically exteriorised in the polar types of leprosy, may be associated with physiological disparity in certain tissue and blood cells. Anti-lymphocytic globulin is reported to enhance the susceptibility of mice to mycobacterial challenge.

The well-known parasitisation of human reticulo-endothelial cells in patients suffering from lepromatous leprosy, has stimulated further work in cell culture and attempts to induce cells from patients already exhibiting failure to lyse and clear mycobacteria, to harbour *M. leprae*. Human skin fibroblasts appear to possess the requisite biochemical and immunological properties to permit such multiplication.

Various adjuvant factors are being investigated in the hope that the ideal substance may one day be found.

'All is not gold that glitters', and mycobacterial strains labelled *M. leprae* in the past are now found to have been incorrectly identified; they mostly belong to the fast-growing mycobacteria differentiable from *M. leprae* by recently developed and more sophisticated laboratory techniques.

Filterable forms of mycobacteria may exist. We need to know more about this possibility.

Morphology and viability, pleomorphism of mycobacteria, L-forms, phenoloxidases and other adjuvant or inhibitory enzymes—all were discussed and notable contributions came from laboratory workers from many countries.

Dr. Weddell's Session (VI) considered the pathology of leprosy with especial reference to its neurological aspects. The most important findings reported were the ultrastructural changes in nerves as revealed by electron-microscopy. There is a growing awareness that immunologically significant changes occur as a response in tissue hypersensitised in some way by mycobacteria or by certain biochemical moieties of their breakdown products. It is not yet possible to distinguish the basis for the extremely varied response at the cellular and at the ultramicroscopical level in leprosy. Is it

pressure? Is it oedema? Is it cellular infiltration? Is it something else? And, whatever it is, what is the fundamental, the ultimate pathology? This may seem to some to be an academic question, but it is of extreme significance to the patient who has leprosy and who is liable to rapid and progressive and irreversible damage to his peripheral nerves with the orthopaedic consequences—paralyses, pareses, anaesthesiae, etc.

Then, in Dr. Hank's Session (VIII), clear evidence was presented that the anergy of lepromatous leprosy was due in part to a subnormal response of leucocytes to physiological stimuli, and to antigens that may be totally unrelated to *M. leprae*. These responses are suppressed by factors occurring in lepromatous serum. The investigations by Dr. Bechelli and others on the Mitsuda reactivity in a non-contact population demonstrated the usefulness of a lepromin containing only 20 million organisms per millilitre, not the 600 million that has hitherto been regarded as the optimum for field work. These results suggested that the lepromin reaction might become positive after the 28th or even the 35th day. This work had been anticipated in São Paulo and elsewhere.

Laboratory investigations disclose further refinements of method for analysing the serological alterations in leprosy and the cross-reactions between *M. leprae* and other related—nearly or distantly related—mycobacteria.

Dr. D'Arcy Hart's Session (X) provided extremely useful data for the continuing debate on the value of BCG vaccination in leprosy.

If BCG does really enhance innate potential resistance to challenge by *M. leprae*, or induce such resistance where it is non-existent, and if it will do this in children exposed intra-familially to such challenge, then this would be the most important single advance in leprosy prophylaxis. If it is true, everybody should know and voluntary organisations and governments should be devoting a high proportion of their resources to controlling leprosy by these means. But wherein lies the truth?—Uganda—80%; Papua and New Guinea—56%; Burma—0%.

Many millions of people are exposed to *M. leprae*, and many will develop leprosy this year, next year and the year after. It is quite impossible to treat adequately and to render non-contagious all patients with lepromatous leprosy in the world within the foreseeable future. If BCG should show the way to prevent leprosy, we beg the epidemiologists to tell us; and meanwhile encourage them to pursue their investigations. In some ways, therefore, this was a disappointing session, not because of the quality of the papers but because of the complexity and the contradictions of the conclusions. It remains for WHO to stimulate further trials, with impeccable statistical control, and severe and critical evaluation; fieldwork, standards and methods must be systemised and correlated, for weighty edifices cannot be built on the collected mass of unreliable primary data. The king-pin in these large-scale investigations is the man working in the field, and not those who, by means of sophisticated instruments, summarise his observations.

It now appears to be established that dapsone, regularly administered to children exposed to leprosy, will protect a high proportion of them against the development of overt lesions.

Dr. Ridley's Session (XII) on the immunological aspects of reaction provided much light and no little heat. Four types of reaction can be identified, which differ in their immunological and prognostic significance, although they have a number of important points in common. Research on their pathogenesis is still in the stage of collecting data. Some promising approaches have produced negative or even inconsistent and contradictory results.

The concept of leprosy as an infection, in which immunity is essentially cell-mediated by lymphocytes, and in which anergy is associated with suppression of lymphocyte production, sheds light on several problems. Reactions associated with an increase of immunity and a movement towards the borderline form of leprosy, may be precipitated in experimental infections in thymectomised mice by injection of normal lymphoid cells. These results represent a distinct advance and, coupled with the work

of Rees and Gaugas at Mill Hill, give us some extremely useful pointers to future research in this aspect of leprosy. It is a well-known fact that *erythema nodosum leprosum* is associated with an increase of complement; immunoglobulins are also increased, and a number of auto-antibodies are sometimes present; but these are no greater in amount—and sometimes are actually less—than in patients with non-reacting lepromatous leprosy. Here again, a problem is presented, and questions are asked that may seem facile to pose but are extremely difficult in practice to answer. The fluorescent antibody techniques (in which many of us pinned a certain amount of faith) are giving inconstant results. *Erythema nodosum leprosum* has a number of parallels with serum sickness, which is due to circulating antigen-antibody complexes.

Dr. Azulay (Session XIV) was concerned with the clinical and practical aspects of leprosy reaction and the therapy of such reaction. The 2 main points brought out in this session were the remarkable progress in the therapy of leprosy reaction, the first being thalidomide, and the second, the Riminophenazine derivative, the aposafranin, B663. With recent memory of its teratogenic and neurotoxic properties, and the knowledge that the legal process against its German manufacturers is now taking place, some practitioners are wary of thalidomide. The drug seems to have a specific anti-inflammatory effect in leprosy reaction and, as Professor Sagher's working party suggests, it is indicated precisely in acutely reacting lepromatous leprosy. The dose recommended is between 100 and 400 mgm. per day; after remission of the acute phase, it may be decreased. The drug has no effect on the disease itself; in fact, its use may be followed by some increase in the leprosy lesions. Some side-effects have been noted, mainly oedema of the extremities and some dizziness and pruritis, but in the main these are not serious. Homologues, derivatives and breakdown products of this drug are being investigated for their possible activity in lepra-reaction. We await with interest further researches along these lines.

B663 is reported to have a definite anti-inflammatory action in the acute exacerbation of lepromatous leprosy. It is active both in the acute exacerbation and also in leprosy itself; in the future it may find its sphere of usefulness in patients with established reaction. It must be given in adequate doses, just as the dose of cortico-steroids are given for their inflammatory-suppressive activity, must vary. It may also be given to patients with severe lepromatous leprosy, especially to those who appear to be prone to develop acute exacerbation. This may prove to be a wide field for this drug; since it may usefully be presented in those situations where it is economically feasible and advisable to give such a drug, e.g., because of the consequences of acute, persistent and prolonged acute exacerbation in lepromatous leprosy in a wage-earner, the head of a family, who has lepromatous leprosy but who wants to be allowed to continue working.

In Dr. S. R. M. Bushby's Session (XVI) the most valuable advance in the field of experimental chemotherapy since the last Congress is the exploitation of the observation by Shepard that *M. leprae* multiplies locally when injected into the footpads of mice. This discovery has produced an experimental model that will permit the determination of the sensitivity of *M. leprae* to drugs suspected of having an anti-leprotic activity. Using this model, Dr. Rees and his colleagues (to whom we now pay tribute) have confirmed that the bacilli from patients who relapse during dapsone therapy are less sensitive to the drug than are those from untreated patients. Truly resistant bacilli, in certain cases, may show cross-resistance with the sulphonamides. Although fully sensitive strains are inhibited by serum levels as low as 0.02 micrograms of DDS per millilitre (which corresponds to a daily dose of 0.1 milligramme for the adult weight 50 kg.), the need for maintaining in the human subject relatively high concentrations is apparent, when it is realised that mycobacteria develop resistance to sulphones by a stepwise process (as has been reported from Baltimore) and that the degree of resistance to the strains from relapsing patients varies within wide limits.

By this method, DDS has been shown to be bactericidal, and there is a distinct difference between bacteriostasis and bactericidal activity. We are grateful to Shepard for developing the kinetic method of demonstrating this difference. It may be that the minimal inhibitory dose may have to be increased many times in the human patient if the emergence of resistant strains is to be forestalled.

Dr. M. F. R. Waters' Session (XVII) concentrated particularly on B663, low-dose dapsone, and long-acting sulphonamides—drugs that together seem to provide some prospect of hope for patients with lepromatous leprosy in rural campaigns who are able to receive a visit from a doctor but infrequently.

The long-acting sulphone, DADDS, may, when given as a single intramuscular injection once every 3 months, produce and maintain a therapeutic blood level of active drug.

The pharmacology and toxicology of B663 were considered at some length; the anti-leprosy activity of the drug is apparently of the same order as that of dapsone. It has been found invaluable in cases of proven dapsone-resistance. The main disadvantage from its use is a ruddy pigmentation of the skin, followed by darkening: these changes of colour tend to disappear slowly when the drug is no longer given.

Dapsone is reported to be active in extremely low doses, such as 5 or 10 mgm. a week, which, however, are theoretically still well above the minimal inhibitory dose. With these low doses, a vigilant watch must be kept for the emergence of drug-resistant strains.

In Argentina it is found that patients with lepromatous leprosy respond more rapidly to sulphonamides than to dapsone, while in Africa some workers have found the long-acting sulphonamides to be particularly valuable in tuberculoid leprosy.

Numerous long-acting sulphonamides are now being synthesised, and it is not outside the bounds of possibility that one day a new compound will be developed that is very much better than the existing long-acting and depot sulphonamides and which can be used in mass treatment campaigns without grave risk of complications and toxic effects. Meanwhile, it is well to remember that these drugs have certain inconveniences and disadvantages, and that they are expensive.

A plea for regular treatment of patients with lepromatous leprosy was reinforced by the report that bacterial negativity could be achieved more rapidly by regular treatment. However, even when approved dose-schedules were followed, the relapse rate in a rural leprosy control scheme concerned mainly with patients with non-lepromatous leprosy, was found to be nearly 5%.

Some work was reported on the newer drugs; ethambutol is effective for a short time; rifamycin was used in a small uncontrolled series with apparently good results. These 2 drugs may open the door to new advances in leprosy therapy, particularly the derivatives and related antibiotics of the latter, some of which show definite and high myco-bactericidal activity.

Several speakers at this session emphasised the need for carefully controlled trials of drugs with suspected anti-leprosy activity, and for comparison with standard dapsone therapy.

In the *concurrent sessions*, extremely important and useful papers were read, and fruitful discussions followed.

Session III (Mr. Hobbs). The ophthalmological aspects of leprosy provoked lively debate. It was reported that many clinicians and many laboratory workers were quite unaware of the dimensions of eye complications. The proportion of patients with lepromatous leprosy who have ocular complications at some time or other in the course of their disease is extremely high. Rarely, ophthalmological manifestations may be the presenting sign of the disease, heralding very serious lepromatous disease, before there are any apparent skin changes. All clinicians should familiarise themselves with the slit lamp, possibly a small portable instrument that can be used by the amateur in the tropical jungles. Every leprologist may not be an ophthalmological specialist, but all clinicians should know how to use a slit lamp. Doctors

were urged to spread knowledge about the ophthalmological complications of leprosy not only to fellow doctors but especially to paramedical workers and nurses. These latter, in fact, are treating over nine-tenths of the patients under leprosy control today, and they should be aware of the early signs of ocular involvement. The early recognition of signs of ocular disorder, very often in the pre-symptomatic stage, is perfectly practicable. For the more highly sophisticated, the budding ophthalmic surgeons, one speaker emphasised that cataract-extraction or keratoplasty, in the past considered unsafe and not worth the risk, can be quite feasible, and is effective in expert hands.

In Professor T. N. Jagadisan's Session (V) emphasis was placed on physiotherapy and its role in the prevention of deformity. Many countries cannot afford a physiotherapy service, but they can afford perhaps one physiotherapist, who can train others. I would beg of you to co-operate with The Leprosy Mission and LEPRA and with certain governments that can afford physiotherapists; invite them, and give them the opportunity of teaching others, not to produce a highly sophisticated (and admittedly rather expensive) reconstructive surgery unit, but encourage them to disseminate knowledge of prevention—prevention of deformity, prevention of ulceration of the anaesthetic feet; prevention is better, and cheaper, than cure. Conservative measures will prevent ulceration of the anaesthetic extremities, and permanent dropping of the feet. Prevention will ensure that the very acutely inflamed nerve will be rested until the phase of oedema is over.

When secondary deformity is established, recourse must be had wherever possible to the surgeons; they provide reconstructive surgery that helps the patient who caught leprosy too long ago, and who has suffered since.

It is not only the orthopaedic, the reconstructive surgeons, who must be enlisted in this task—as they do their Cockett's operation on the nose, and post-nasal inlays, and the rest—but also the 'jobbing surgeon' who is confronted by row upon row of people with ulcerated and dropped feet, with sagging faces, and with paralysed ulnar nerves. Jobbing surgeons can do much, provided they do not spend time and energy attempting to perfect their surgery while allowing thousands of patients in the villages to develop deformities. When secondary deformity has occurred, however, there is a real need for the co-operation of the prosthetist, the footwear maker and the occupational therapist.

As far as physiotherapy is concerned, of course, the selection and preparation of patients for tendon-transfer surgery is all-important. In order to obtain the maximal post-operative functional capacity, with good appearance, the active co-operation of the patient with the physiotherapist, and the surgeon, and the prosthetist is essential. These skills must be shared with the ordinary poly-competent paramedical worker, who is responsible for most of the leprosy treatment in the world today. It is he who mediates our skills and educates the patient in the protection of anaesthetic extremities, and it is he who helps the patient back to life and health again.

Dr. Molesworth's Session (VII) had to confess that successful leprosy control is achieved but rarely. This failure is in part a reflection on us, and on governments for not making more money and more people available; but, in any case, much more should be done. The integration of leprosy services with existing services and the training of paramedical workers were repeatedly stressed.

The speakers took note particularly of the time consumed and the proportion of finance involved in institutional care. Some countries can afford it; most cannot. And where intensive campaigns are in progress, a great increase in the number of registered cases occurs. Leprosy is always far more prevalent than is realised on initial surveys.

The surgeons had most stimulating meetings, with Brand and Antia contributing magnificently through their Sessions (IX and XI) to the application of reconstructive surgery to the patients who caught leprosy too long ago, or who were inadequately treated. They emphasised the value of visits from one country to another,

from one surgical group to another; they considered various technical matters such as the excision of metatarsal heads for persistent ulceration of the forefoot.

At the close of Session IX, the place of surgery in leprosy control programmes was considered. In New Guinea it was demonstrated how a single surgeon, working out from a base hospital, can carry out 'surgical camps' in a large number of small general hospitals. In each centre, there is a trained auxiliary who carries on before and after the visit of the surgeon. Therefore, post-operative and pre-operative treatment can be given, and the evidential value of these expert visits has to be seen to be believed. This system has resulted in general hospitals becoming willing to co-operate, first in the rehabilitation programme and later in leprosy control. This is, in other words, a practical demonstration, through the surgeons, of what should be done and what can be done. The surgeon has thus built a bridge between the highly-specialised orthopaedic and reconstructive surgery unit and the leprosy team and the ordinary patient in the villages scattered in the remote mountain valleys of Papua and New Guinea.

In Dr. Antia's Session (XI), there was some excellent discussion on certain surgical aspects of nerve-pain and the prevention of paralysis, but the greatest interest was evoked by reports on the pathology of nerve damage in leprosy—nothing new, but all very stimulating. Not only nerves, but smooth muscle cells are now seen to be microscopical sites of predilection for *M. leprae*.

The psychological aspects of leprosy provided a varied programme in Session XIII (Chairman: Dr. Oliver W. Hasselblad). The main conclusion was that there is much ignorance—ignorance among doctors and paramedical workers, among administrators, among leprosy patients themselves and the community. Much more must be done to investigate psychological attitudes of the individual patient and of the community in which he lives, so that, eventually, the stigma of leprosy will disappear and leprosy will be treated in the patient's inner mind, as well as in the community, as a disease, like other diseases. Results from Bombay, as well as from the United States of America, stressed these findings. Confidentiality should be preserved at all points and secrecy must be maintained, but a tremendous amount needs to be done to help the leprosy patient from becoming dependent on the community and isolated from that community.

In Session XV (Mrs. Weaver) several interesting papers were presented that covered familiar ground and emphasised old truths in new ways. While some countries are able to report a certain progress in leprosy sociology and the acceptance by society of the fact that leprosy exists, and the associated and often equally unpalatable fact that those who suffer from leprosy are indeed human beings and should be treated as such, elsewhere the stigma dies hard and the unwarranted aura of superstition and folk-lore shows little sign of dispersing.

The urge to social rehabilitation often depends on the informed enthusiasm of the individual—in government service or in a voluntary organisation. Planning is essential, but impersonal planning may defeat its own end; much depends on the drive and personal sympathy of those in charge.

The knowledge that social services are available, that discrimination is officially frowned upon, that employment for the patient and support for his family are assured, may do much to augment and strengthen any anti-leprosy campaign. It is in the relatively wealthy countries, and in urban and sophisticated communities, that these welfare and social services are not only working but are seen to be most effective. Nevertheless, in the developing countries, with their larger and less tractable leprosy problem, rural rather than urban, such schemes for the rehabilitation of the leprosy patient are no less essential.

Much discussion was aroused over the proposal to abolish the word 'leprosy', and to replace it by an eponymous or neutral scientific descriptive term, but some contributors were of opinion that the *disease* rather than the *name*

of the disease needed rehabilitation, and that all efforts should be bent towards education of the public, the medical profession (including medical students) and politicians in the true nature, importance and curability of this widespread and crippling disease.

Dr. Davey's Session (XVIII) on 'Co-operation and Priorities' attempted to translate into the humdrum world of practical politics the scientific advances now available, and to relate the leprosy problem to the human and material resources at our disposal. The essential intractability of leprosy as a disease of the physical nature of man—with its non-material overtones—renders any piecemeal attack abortive and ineffective. We are dealing with persons, living in a social environment and conditioned by many and diverse factors. If existing knowledge could be applied on a world scale, even though many of the answers to the problems leprosy poses still elude us, then the slow spread of leprosy could be halted. More emphasis should be placed on well-planned leprosy control schemes, integrated wherever possible with general health measures. Unless and until the huge reservoir of patients with 'open' leprosy is tackled realistically and co-operatively, then the endemic will continue to smoulder.

The session ended with a plea for co-operation—between governments and voluntary agencies, between national and international agencies, between the more affluent and the poorer countries of the world, between the research scientist and the field worker. Co-operation is also necessary between those engaged in all aspects of leprosy, and those coming into leprosy from other branches of science. Given these priorities, and this degree of co-operation, leprosy could be 'controlled in our generation and eradicated in the next'.

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Mycobacterium leprae in Muscle

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INTRODUCTION

There are few references in the literature to the presence of *M. leprae* in muscle.

The earlier references (Babes, 1901; Klingmüller, 1930) describe *M. leprae* in the vicinity of, but not within, smooth muscle in the dermis —the arrectores pilorum muscle. More recently, Neves (1961) reported that bacilli and globi were frequently to be found between the fibres of these muscles. Hashizume and Shionuma (1965), in an electron microscopic study of lepromatous changes in the iris, reported finding *M. leprae* in and between the smooth muscle cells of the iris. Also in an electron microscopic study of leprosy lesions, Nishiura *et al.* (1960) reported the finding of *M. leprae* in the smooth muscle cells of blood vessels.

There are still fewer references in the literature to the presence of *M. leprae* in striated muscle. Ishihara (1959) reported 4 cases with myositis interstitialis leprosa where lepromatous infiltration was present between striated muscle fibres. Convit *et al.* (1960) reported 4 cases of lepromatous myositis in which *M. leprae* were found in lepromatous infiltrate between striated muscle fibres; they also stated that most of the bacilli stained irregularly. Some bacilli, however, were found within muscle cells, and some of these were solid staining.

PERSONAL OBSERVATIONS

In this Centre, only a few opportunities of examining biopsies of striated muscle taken from the limbs of lepromatous patients have presented themselves during the past few years. In none of these have bacilli been seen in muscle fibres, although they were found in the neurovascular tissue and in accumulations of histiocytes between muscle bundles.

By contrast, in biopsies of skin and other tissues, bacilli have been found not only between smooth muscle cells but also within the cells themselves. Furthermore, it is noted that in patients undergoing treatment with dapsone (DDS) or other antileprosy drugs, the bacilli in the muscle cells may stain less irregularly than those in the surrounding infiltrate. Such bacilli are found both in the arrectores pilorum muscles and in muscle fibres in the walls of the larger blood vessels. Organisms in these sites might be the origin of the relapses that may occur when treatment is stopped before it should be. Thus, in biopsies obtained from patients with lepromatous or near-lepromatous leprosy, when the skin smears no longer contain bacilli, we at this Centre habitually look for bacilli (particularly solid staining forms) in smooth muscles in the skin.

In biopsies from the face, deep enough to include bundles of striated muscle, no bacilli were found in any of the muscle fibres examined, although they were present in the infiltrate and neurovascular tissue between them, and in the overlying arrectores pilorum muscles.

It would thus appear that, in man, smooth muscle, rather than striated muscle, may be a preferential site for the multiplication of *M. leprae*. It is, therefore, considered important to publish details of some unusual findings in biopsy material containing smooth muscle sent for examination to this Centre.

BIOPSY 1. Received in August, 1967, from Uganda. The specimen came from a male with active lepromatous leprosy who was receiving dapsone. Circumcision had been advised on clinical grounds. At operation, a small mass was found in the foreskin; the whole of the excised foreskin was therefore put in fixative and sent for microscopical examination. A report was requested on the nature of the mass, which was suspected to be either a lepromatous nodule or a tumour. On examination, the mass was indeed a lepromatous nodule, but it was noticed that

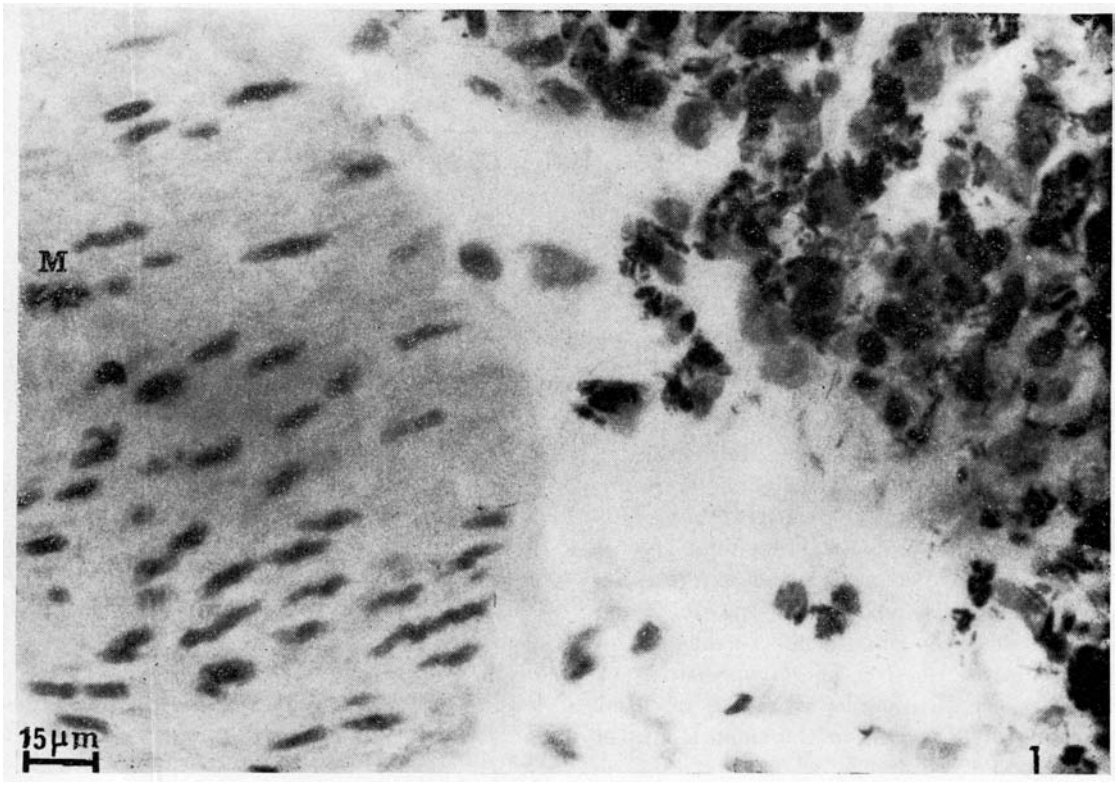

FIG. 1

Human foreskin. Two obliquely cut smooth muscle bundles. One fibre in healthy bundle, left, contains a micro-colony of solid-staining *M. leprae* (M). Neighbouring muscle bundle, right, nearly exhausted, contains irregularly staining *M. leprae*, lymphocytes and plasma cells.

the foreskin contained a large number of smooth muscle bundles. *M. leprae* were present in considerable numbers in the lepromatous infiltrate, most of them staining irregularly with carbol fuchsin. Many of the muscle bundles also contained bacilli, most of them apparently lying within muscle cells; by contrast, most of these organisms were solid staining (Fig. 1).

Because of this finding, biopsies were requested from this same patient of skin from the scrotum for the dartos muscle, from the face for facial muscle, and from the forearm to include some of the underlying striated muscle. Meanwhile the patient experienced episodes of acute reaction; the dose of dapsone had consequently first been decreased, and then stopped altogether.

The small piece of striated muscle from the forearm was found not to contain bacilli. Nevertheless, in the overlying skin and arrectores pilorum muscles numerous bacilli were present. Comparable observations were made in the biopsy containing muscles of the face, but here bacilli in the arrectores muscles were fewer than in the forearm. Numerous bacilli were present in the lepromatous infiltrate in the scrotal dermis and in the dartos muscle bundles. Some dartos muscle fibres contained micro-colonies of *M. leprae*, and others globi of solid-staining bacilli contained in vacuoles within the sarcolemma (Fig 2).

In all the specimens examined from this patient, it was noteworthy that no inflammatory cells could be seen invading or surrounding the solid-staining bacilli present within the bundles of smooth mucles. Those bundles in which the bacilli were most numerous and which were most disorganised, however, did contain in-

FIG. 2

Human scrotum. Smooth muscle fibres containing numerous solid-staining *M. leprae*. No inflammatory cells are present.

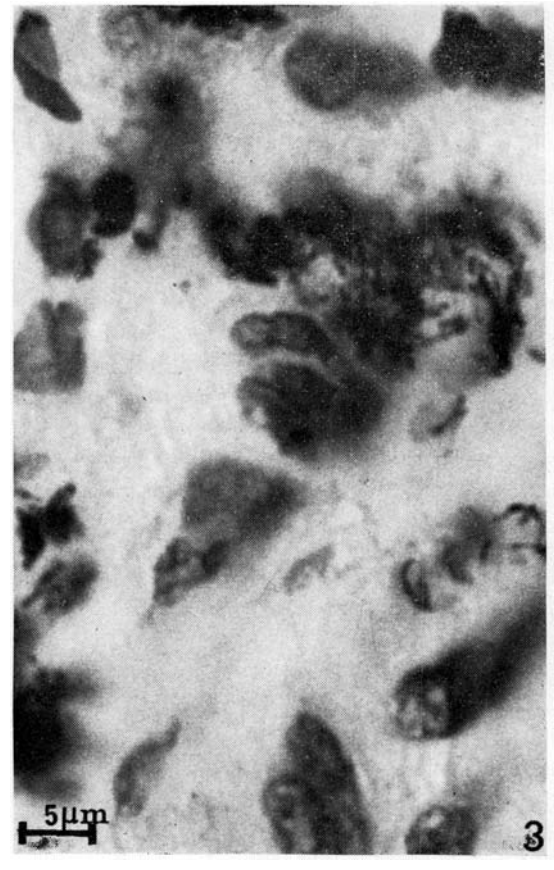

FIG. 3

Human nipple (male). Exhausted smooth muscle cells. Inflammatory cell nuclei lie close to irregularly staining *M. leprae*.

All Figs. are from sections stained with haematoxylin and cold carbol fuchsin.

flammatory cells invading and around them. Even in these bundles, solid-staining bacilli were present in the muscle fibres that were still intact.

BIOPSY 2. Received August, 1967, from Nepal. This specimen was from a male patient with active lepromatous leprosy, who had gynaecomastia. The biopsy included part of the nipple, containing bundles of smooth muscle. Solid staining bacilli were seen in those muscle fibres that were intact; muscle bundles with intact fibres containing bacilli were neither surrounded nor invaded by inflammatory cells. Exhausted muscles were full of irregularly staining bacilli, and contained inflammatory cells (Fig. 3).

DISCUSSION

It is well known that *M. leprae* multiply in Schwann cells, where they may be temporarily immune from attack by lymphocytes and plasma cells. By contrast, when present in histiocytes, they are usually surrounded by inflammatory cells and are seen to be undergoing digestion. The observations reported above suggest that protection is also afforded to organisms in smooth muscle cells. This would appear to be an important finding, since organisms in nerves and smooth muscle are not

so likely to be sampled in smears as are those in lepromatous skin infiltrate. In some cases, falsely low values for the Bacteriological Index (B.I.) and the Morphological Index (M.I.) may well be obtained. If solid-staining organisms are confined to sites from which smears are never taken, e.g., the scrotal dartos muscle, or the small voluntary muscle fibres in the palm of the hand or the sole of the foot, then the B.I. and the M.I. from skin smears may be even more misleading. These findings may account for the relapses that occur in patients taking dapsone irreguarly, or who stop taking dapsone before they should. Under such conditions, the living organisms in smooth muscle and Schwann cells might well begin to multiply without restraint and then to spread throughout the body.

These observations suggest that leprosy workers should be on the look-out for solid-staining bacilli in smooth muscle in all patients suffering from leprosy that is towards the lepromatous end of the spectrum. Smooth muscle is abundant in the scrotum, in facial skin and in other hairy skin sites. Care should, therefore, be taken to include hair follicles in skin biopsies.

It is not yet known if *M. leprae* are able to multiply more readily in smooth than in striated muscle in man. The observations of Rees and Weddell (1968) that *M. leprae* multiply and are found in large numbers in certain striated muscle fibres of mice, immunologically crippled by thymectomy and total-body irradiation, are of interest and importance. Leprosy bacilli may well reside and multiply in striated muscle in man, but it will be difficult to obtain sufficient biopsy material to test this hypothesis. However, Rees and Weddell (1968) have already reported, in a preliminary study, that bacilli are present in striated muscle in a proportion of patients with lepromatous leprosy. Current work (Rees and Weddell, 1968, personal communication) suggests that they probably multiply only in one kind of striated muscle (B fibres) in mice, and this may well be the case in man also. Until this supposition is confirmed, skin biopsies that include smooth muscle are to be preferred to those that do not.

ACKNOWLEDGEMENTS

I am greatly indebted to Dr. A. G. M. Weddell, Department of Human Anatomy, Oxford, and to Dr. R. J. W. Rees, National Institute for Medical Research, Mill Hill, London, for their guidance and assistance in the writing of this article, and for the preparation of the photographs.

I also wish to thank Dr. G. J. D. Moore, formerly Medical Officer at Kumi Leprosarium, Uganda, and Dr. J. C. Pedley, Leprosy Mission, Tansen, Nepal, for the biopsy material they sent.

Finally, I am most grateful for advice and technical assistance from my colleagues at the Leprosy Study Centre, Dr. S. G. Browne, Director, and Mr. E. A. Wheeler, Laboratory Technician.

FOOTNOTE

While this article was being prepared for the press, attention was directed to the paper by Job *et al.* entitled 'Leprous myositis—a histopathological study,' which appeared as Abstract No. 137 in Session XI in the Ninth International Leprosy Congress, London, 1968, and which is to be published in the *International Journal of Leprosy*, Vol. 26, No. 4 (II). In this paper, Job reports the finding of *M. leprae* in the fibres of striated muscle, but more abundantly so in the fibres of smooth muscle, particularly those which are subcutaneously placed.

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The presence of *M. leprae* in the Lumina of the Female Mammary Gland

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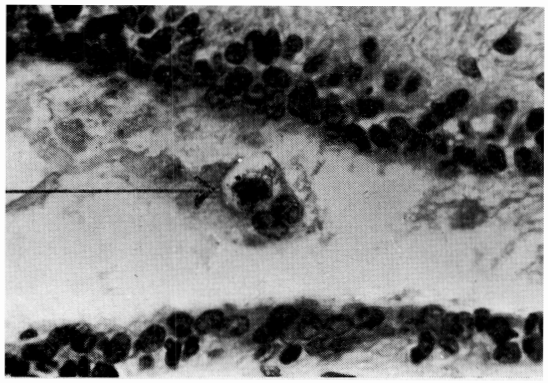
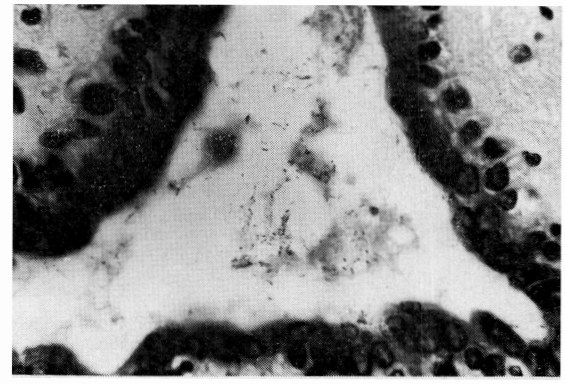


A

M. leprae in globus arrangement (see arrow) in the lumen of a mammary gland.



B

M. leprae in irregularly staining form in the lumen of a mammary gland duct.

The purpose of this brief article is to report the finding of *M. leprae* in the lumina of the mammary gland of a woman whose case was described in a previous paper[1] before this finding had come to light.

Ten weeks after the discovery of *M. leprae* in the breast secretion of this woman (during which time 450 mgm. of DDS had been administered), the writer took a biopsy from the glandular portion of the right breast at approximately 2 cm. from the areola margin.

HISTOPATHOLOGY (see accompanying photomicrographs)

Sections of the biopsy, stained with Triff Stain, showed a scattering of numerous acid-fast bacilli—most of which were in non-solid staining form—in the lumen of a lactiferous duct cut in longitudinal section. Other groups of fragmented bacilli were present in cellular debris shed into the lumen of ducts, and an occasional irregular staining bacillus was present between the cells lining the ducts. In one duct cut in longitudinal section a large globus full of fragmented bacilli was present in the lumen. Occasional fragmented bacilli were also found in the lumina of atrophied alveoli. In contrast to the very obvious presence of bacilli in the lumina of the gland, the bacilli in the intervening tissue between the ducts and alveoli were very scanty.

DISCUSSION

The appearance of the bacilli in the biopsy section—mostly in fragmented form—compared with those seen 10 weeks previously in the breast secretion[1] when the majority were in solid rod form, seems to prove the efficacy of DDS treatment in rapidly reducing the bacilli to insignificance. The same conclusion was reached in the continuation notes of the writer's former paper describing the presence of *M. leprae* in human milk[2]. There, 450 mgm. of DDS, administered over a period of 3 months, also reduced the bacilli in the milk to insignificance.

ACKNOWLEDGEMENT

I am indebted to Dr. D. J. Harman of the Leprosy Study Centre in London for having sections of the biopsy made, and for the accompanying photomicrographs.

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Lep. Rev. (1968) **39**, 4, 203-206

Trials with Thalidomide Derivatives in Leprosy Reactions

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INTRODUCTION

The suppressive effect of thalidomide (N-thalimido-glutarimide) on lepra reactions has been proven by comparison with a placebo in direct and in double-blind studies[1 2 3 4]. The purpose of the present study was to establish whether 1-morpholinomethyl-4-phthalimido-piperidindion-2,6 (CG603) and 1-morpholino-methyl-3-phthalimido-piperindion-2,6 (CG601), both derivatives of thalidomide, are also active.

MATERIALS AND METHODS

Five patients with lepromatous leprosy and lepra reactions were treated (Table 1).

M. leprae was present in all patients. Histological findings were in accord with the clinical picture. The Mitsuda test was negative. Of the 2 female patients, one was post-menopausal and the other a virgin. Both were continuously under gynaecological and laboratory supervision.

The patients had previously received specific treatment consisting of diaminodiphenylsulfone (DDS), diphenylthiourea (Ciba 1906), thio-semicarbazone (or TB). Previous treatment of the lepra reaction had been with antimony, steroids and thalidomide.

CG603 was given in a dose of 500 mgm. 4 times daily for 6 days. CG601 was given in a dose of 50 mgm. 4 times daily for the same length of time. These doses were in accordance with the manufacturers' recommendations. Tablets were enteric coated. Treatment was administered in separate, consecutive series, with an interval of at least 10-20 days between each series.

RESULTS

CG603, given to 4 patients in 4 trials did not influence the lepra reaction and was considered therapeutically inactive in our 4 patients.

Thirteen trials with CG601 were carried out in 5 patients. These comprised 5 trials in one patient; 3 each in 2 patients; and one each in 2 patients. In 8 trials that lasted for a longer time, reducing the dose below 100 mgm. or, in one trial, withdrawal of the drug, was followed by a relapse. In one patient CG601 was given for 10 months, during $4\frac{1}{2}$ of which the treatment was combined with sulfones. There were no new lesions in the skin.

Within the first 24 hours of treatment with CG601 there was improvement in the general condition and the patient subjectively felt better. In the next 48 hours there was resorption of the reactional skin lesions, and of the inflamed nerves. Pains diminished as did the articular symptoms. Appetite and sleep improved and the patients appeared more restful. Blood count, blood proteins, liver function tests, blood electrolytes, blood glucose, urea and transaminases remained normal during the trial periods. The blood sedimentation rates, high in all 13 trials, decreased in 4 of them from 107 to 77 mm. on one occasion, from 88 to 9, from 78 to 52 and from 50 to 30 mm. on 3 other occasions. In 9 trials there was no change in the blood sedimentation rate.

TABLE 1

Patients with Lepromatous Leprosy and Lepra Reactions treated in the present study

Patient	*Sex*	*Age*	*Duration of Leprosy (in years)*	*Duration of Lepra Reaction (in years)*
1	M	31	25	24
2	F	25	16	15
3	M	21	3	3
4	F	53	4	4
5	M	56	7	7

There were no changes in the lepromas. Bacteriological studies remained positive. There were no side effects even in the patient who received the drug continuously for 10 months.

Two case reports are presented in detail:—

Patient 1: E.D., a 31-year-old man with lepromatous leprosy of 25 years' duration. He had lepromas and lepra reactions and azoospermia. He had received treatment with oil of chaulmoogra, thiosemicarbazone 50-150 mgm./day, sulfones 50-100 mgm./day and diphenylthiourea 2-4 gm. daily. During the first several years of his illness he had had an almost continuous lepra reaction which had been treated with antimony and steroids. In the past 3 years he had had only 4 lepra reactions. During 3 of these he received thalidomide for from 5 to 12 days. The dose was 400 mgm. daily and the free interval from lepra reaction lasted up to 17 months. The last reaction consisted of erythema nodosum leprosum with erythema multiforme of the face, chest and extremities. There was also neuritis, arthralgia, insomnia and lack of appetite. He had a temperature of up to 39.7°C. The blood sedimentation rate was 58 mm./h. He received 2 gm. CG603 daily in addition to sulfones. No improvement ensued during the 6 days of the trial. New skin lesions appeared on the extremities and chest. His temperature rose up to 40.2°C. The blood sedimentation rate was 100 mm./h. and there was subjective deterioration.

The CG603 was discontinued and CG601 was administered. Within 24 hours the temperature dropped to 37.8°C. The skin lesions and neuritis regressed and were almost completely resorbed on the sixth day of treatment. The blood sedimentation rate fell to 52 mm./h. The blood count was normal before CG601 was given and did not change.

Patient 2: N.D., a 25-year-old virgin, was hospitalised continuously for 16 years because of nodular and reactional manifestations. At various times during a period of 8 years she received 25-100 mgm. sulfones and 25-5 mgm. of meticorten per day.

She was never free from lepra reactions for intervals longer than 3-4 weeks. She was given thalidomide 200-300 mgm. initially and when no improvement ensued the dose was increased to 500 mgm. At this dose there was definite improvement, and the dose was decreased gradually to 100 mgm. daily, and for a year she was free from reactional manifestations. Relapses appeared with lower doses. After a year thalidomide was stopped and sulfones were continued. Two weeks later a lepra reaction occurred. She was given CG603 for 6 days without effect; new elements of erythema nodosum leprosum appeared and she also had neuritis, arthralgia and a fever of 39°C. The BSR was 72 mm./h., Hb 11.8 gm.%, hematocrit 35%; leukocyte count and liver function tests were normal. At this stage 150 mgm. of CG601 was given. Within 24 hours the temperature dropped to 38°C. Skin lesions began to fade, and her neuritic pains and arthralgias subsided. On the seventh day there were no lepra reaction lesions to be seen.

The BSR dropped to 30 mm./h., Hb rose to 13.3 gm.%, hematocrit to 40%. The patient received CG 601 for 10 months; for 4½ of these, treatment was combined with sulfones. The dose of CG601 was reduced to less than 100 mgm. per day on 4 occasions and each time a reaction promptly appeared. Stopping the drug was followed by an acute reaction, that responded to a daily dose of 150 mgm. CG601.

DISCUSSION

After the promising results obtained with CG601 it became important to establish whether the drug could prevent lepra reactions present in patients on sulfone treatment. It was found that 100 mgm. per day was the minimum maintenance dose in such circumstances.

In the present study the maximum dose of CG601 was 200 mgm. per day. This could account for the slowness of improvement as compared with that of thalidomide, which was given initially at a dose of 400 mgm. daily.

The pharmacodynamics of CG601 are unknown; they may resemble those of thalidomide.

SUMMARY

1. CG603 and CG601 were tried in 5 patients with lepra reactions of long standing.

2. Four patients received up to 2 gm. of CG603 daily for 6 days. There was no effect on the lepra reaction and the use of the drug was stopped.

3. Thirteen trials with a daily dose of 900 mgm. of CG601 were carried out. Five trials lasted 6 days and 8 up to 10 months. There was a beneficial effect on lepra reactions. Lowering the dose below 100 mgm. daily often resulted in a relapse.

4. There was a definite subjective and objective improvement, starting in from 24 to 72 hours. The improvement seemed to be slower than that induced by thalidomide.

5. No side effects were observed during the trial period.

CONCLUSIONS

1. In a short clinical trial on 4 patients with lepra reaction 1-morpho-linomethyl-4-phthalimido-piperidindion-2,6 (CG603) appeared to be ineffective.

2. In 13 separate trials performed on 5 patients, 1-morpholinomethyl-3-phthalimido-piperindion-2,6 (CG601) had a beneficial effect both subjectively and objectively on lepra reactions.

3. A larger scale trial of the latter drug in lepra reactions appears justified.

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Treatment of Acute Exacerbations in Leprosy with Indomethacin

A PRELIMINARY REPORT

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Indomethacin, a new non-steroidal agent, has come into prominence in recent years as a useful anti-inflammatory, anti-pyretic and analgesic drug in the treatment of certain inflammatory joint diseases like rheumatoid arthritis, gout, ankylosing spondylitis, oesteoarthritis, etc. In these conditions this drug has been found to be as effective as other commonly used agents like corticosteroids, salicylates, phenylbutazone, etc. Unlike corticosteroids, indomethacin has no effect on pituitary or adrenal function, and when given concomitantly with corticosteroids, the dosage of the steroids can often be reduced. Silberman *et al.* (1965) found that indomethacin could be a useful adjunct in the symptomatic treatment of fever in Hodgkin's disease, lupus erythematosus, etc.

The foregoing experience prompted a clinical assessment of the anti-inflammatory and analgesic properties of indomethacin in the treatment of acute exacerbations of leprosy.

MATERIAL AND METHODS

Patients suffering from leprosy of all types with predominantly skin manifestation of the type of erythema nodosum leprosum (ENL) or tuberculoid lesions in reaction and those with polyneuritic involvement with marked pain and thickening of ulnar and peroneal nerves were selected for the study.

Thirty-one patients (28 males and 3 females) in the age group of 12 to 35 years were included in the trials. The type of leprosy was lepromatous in 19 patients, intermediate in 5, and tuberculoid in 7.

All the lepromatous and intermediate groups of patients were strongly positive bacteriologically; and 19 out of 24 such patients had shown recurrence of lepra reaction on several occasions and had received calcium gluconate with antimonials or antimalarial drugs for each exacerbation. Five patients were experiencing reaction for the first time.

The tuberculoid patients were bacteriologically negative. Most of the patients with severe neuritis had been treated earlier with oral analgesic drugs with or without local ethyl chloride spray or perineural injections of hydrocortisone, or intradermal injections of 'hydnocreol' along the course of the nerve.

The dose of indomethacin (25 mgm. per capsule) and duration of treatment varied in different patients depending upon the clinical response. In the majority of the patients a maximum of 100 to 150 mgm. in 3 or 4 divided doses was maintained daily after an initial period of treatment with 75 mgm. per day. After a varying period of treatment the dose was tapered off to 50 mgm. per day before stoppage.

The duration of treatment varied from 3 to 30 days except in one patient who was treated for a total period of 64 days intermittently to study the analgesic effect of the drug on neuritis. The majority of the patients received treatment for 7 to 12 days.

Most of the patients were admitted into the ward and a careful clinical assessment of the response of skin lesions during treatment was made. Record of their progress regarding regression of fever, neuralgia, arthralgia, etc., was made. Adverse symptoms, if any, attributable to the drug were recorded.

TABLE 1 **Showing response of Neuritis to Indomethacin**

Type	*No. of Patients*	*Marked Response*	*Moderate Response*	*No Response*
Lepromatous	10	5	3	2
Intermediate	3	3	Nil	Nil
Tuberculoid	6	4	2*	Nil
Total	19	12	5*	2

* Two patients with ulnar nerve abscess.

TABLE 2 **Showing response of skin lesions in Reaction to Indomethacin**

Type	*No. of Patients*	*Complete Regression*	*Partial Regression*	*No appreciable Change*	*Aggravation of Lesions*
Lepromatous	18	2	5	2	9
Intermediate	5	2	1	Nil	2
Tuberculoid	1	Nil	Nil	Nil	1
Total	24	4	6	2	12

RESULTS AND DISCUSSION

The tables show that the best results of the drug are obtained in patients with severe neuritis especially those belonging to the intermediate or tuberculoid types of leprosy.

The analgesic property of the drug was evident in the few cases of tuberculoid leprosy with unilateral ulnar neuritis resulting in marked limitation of movement of elbow joint. Often there was subjective sense of improvement due to relief from pain, and joint movement was restored.

However, the results obtained in the case of skin lesions in reaction were not encouraging. There was improvement in 10 patients but in 12 others the lesions were aggravated, the ENL lesions becoming more erythematous and sometimes undergoing necrosis. These findings are in line with the observations of García Fernandez (1965). In 2 patients no response was evident.

An objective assessment of the antipyretic effect of the drug was not possible as the majority of the patients in this trial did not have high fever. However, García Fernandez (1965) and Thiers *et al.* (1966) have reported that indomethacin is highly effective as an antipyretic in acute exacerbations of leprosy.

The side effects of indomethacin in the dosage employed in this study were minimal and, in general, drug tolerance was very satisfactory. Three patients (one of whom had blurred vision) complained of giddiness 6 to 7 days after administration of the drug, and this symptom was relieved after withdrawal of the drug.

SUMMARY

The results of this preliminary clinical trial with indomethacin in acute exacerbations of leprosy indicate that the drug is an effective analgesic in producing symptomatic relief of neuralgia and arthralgia. The skin lesions, however, do not respond favourably and may, at times, be aggravated. The drug was well tolerated and there were very few side effects.

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The Use of the Voluntary Muscle Test in Leprosy Neuritis

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There are 2 main problems in leprosy, the presence of leprosy bacilli and the presence of deformity. Except in the rare instances where deformity follows lepromatous infiltration of skin or bones, deformity in the limbs is secondary to involvement of peripheral nerves by the leprosy disease process. Cochrane (1964) has emphasised that unless neuritis is 'taken in hand at once, serious and crippling deformity is likely to result'. While many measures have been suggested by leprologists to reduce nerve pain, the need to assess the function of inflamed nerves and note whether treatment improves or lessens function is rarely mentioned. Criteria for assessing the results of treatment of acute ulnar neuritis in leprosy have been suggested by Harris (1964). He recommends a battery of sensory and motor tests, but for the latter prefers to measure the strength of pinch and grasp with a 'pinchometer' and a 'dynamometer', rather than to test individual muscles. However, these instruments do not distinguish between the muscles supplied by the ulnar and median nerves, and only one of these nerves may be involved at any one time in a leprosy patient. Testing the strength of individual muscles by the Voluntary Muscle Test has long been recommended for assessment of nerve function in peripheral nerve lesions (Report, 1943). If the nerves of all leprosy patients are palpated at the sites where thickening and tenderness commonly occur, a high proportion of these patients may be found to be suffering from acute or subacute neuritis. Thus a rapid, reliable and reproducible test of nerve function is required, which can be repeated serially. During the last 7 years the author has employed the Voluntary Muscle Test, also known as the manual muscle test (Daniels *et al.*, 1956), to assess nerve function in leprosy neuritis; and has requested physiotherapists and physiotherapy auxiliaries to perform this test in Hong Kong, England and Ethiopia. Orthopaedic surgeons and physical medicine specialists not infrequently use the Voluntary Muscle Test to assess recovery of nerve conduction (Mannerfelt, 1968).

It is the object of this paper to show that the Voluntary Muscle Test (V.M.T.) has considerable value in the assessment of leprosy neuritis and the results of treatment. It is not suggested that the V.M.T. is a substitute for sensory training; and where sufficient staff exist many different tests of nerve function can be usefully performed, including electromyography and nerve conduction studies. Parallel electrical tests and V.M.T's were performed in one leprosy patient, and the relative value of these assessments is presented. During the last 7 years the author has continually revised the descriptions of the methods of testing each muscle, especially in the hand; and these descriptions of muscles most useful for assessment of nerve function, together with an indication of the muscles found to be most reliable are included in this paper. The descriptions and uses of V.M.T's of all hand and foot muscles will be the subject of another paper (Watson, to be published).

MATERIALS

In the Leprosy Mission leprosarium of Hay Ling Chau in Hong Kong from 1962 to 1964, 166 patients with acute neuritis were studied and

treated. These included men and women, and 95% were aged between 14 and 50 years of age. Voluntary Muscle Tests (V.M.T's) were done serially on all these patients at intervals varying from 3 weeks to 2 months. During 1966 and 1967, serial V.M.T's were done on 2 leprosy patients in England, one of whom was also subjected to electromyography and nerve conduction studies. In Ethiopia since September, 1967, over 200 patients with acute neuritis have been studied and treated with the aid of the V.M.T.

METHODS

Leprosy patients may draw attention to their early neuritis by complaining of nerve pain, anaesthesia or paraesthesiae, but many patients in developing countries with neuritis do not complain of nerve symptoms. One of the simplest methods for recognising early leprosy neuritis is to palpate the peripheral nerves of all leprosy patients at the sites where swelling and tenderness usually occur. The most commonly affected nerves in the arm are the ulnar at the elbow, the median just above the wrist, the radial palpable in the spiral groove, and very occasionally the median at the elbow. In the leg the lateral popliteal nerve at the head of the fibula and the posterior tibial nerve at the ankle are the most commonly affected. Any *tender nerve* should be rapidly assessed by the doctor or health worker for sensory and motor loss in the area supplied by that nerve; and in the absence of complete paralysis a request is made to the physiotherapist or physiotherapy auxiliary to perform a V.M.T. on the muscles supplied by each inflamed nerve.

Hands that appear normal in shape and function when examined by a casual observer may be found to be unable to perform a pulp-to-pulp, thumb-to-little finger pinch; or there may be an inability to hold a piece of paper tightly between the extended ring and little fingers. When there is median neuritis, weakness of the abductor pollicis brevis may be found by a rapid test of that muscle. Patients with any of the above signs are referred for a V.M.T.

VOLUNTARY MUSCLE TEST TECHNIQUE FOR THE HAND

The Medical Research Council scale of strength of muscles (Report, 1943) is used, modified slightly in the case of strength grade 2 to a 'less than full range' rather than 'movement with gravity eliminated', as the effect of gravity in the hand is negligible:—

5. Full strength against resistance provided by the assessor's hand or finger.
4. Movement against some resistance is possible, range of movement is full.
3. There is a full range of movement, not possible against resistance (but can be done against gravity).
2. There is less than a full range of movement.
1. A flicker of movement or muscle contraction seen or felt on attempted movement, but no actual joint movement.
0. No movement.

M.P. joints = Metacarpophalangeal joints.
P.I.P. joints = Proximal interphalangeal joints.
D.I.P. joints = Distal interphalangeal joints.

General note: Whenever possible the strength and movement of the 2 hands are compared to detect small degrees of weakness. *Italicised* muscles can be accurately tested, and if these muscles alone are tested, then a reasonably accurate picture of the state of paralysis can be gauged. Resistance is always given in the direction opposite to the movement being attempted by the patient. Before applying resistance it must be first assessed whether the range of movement is full.

MUSCLES USUALLY SUPPLIED BY THE ULNAR NERVE

Flexor carpi ulnaris (F.C.U.). With the palm up, the patient flexes the wrist with ulnar deviation. The assessor feels for the muscle tendon just proximal to the pisiform bone.

Flexor digitorum profundus (*F.D.P.*) to the ring and little fingers. With the patient's palm up, the assessor maintains extension of the M.P.

and P.I.P. joints of the finger being tested, and all joints of the other fingers. The patient then flexes each D.I.P. joint. Resistance is applied by pressure to the pulp of each finger in turn.

Abductor digiti minimum (*A.D.M.*). With the palm up, the little finger is flexed slightly at the M.P. joint and abducted, keeping the other joints extended. Resistance is applied by pressing the little finger towards the finger-adducted position.

Opponens digiti minimi (O.D.M.). With the palm up, the little finger is flexed slightly at the M.P. joint and deviated radially keeping the finger straight.

1*st dorsal interosseous* (*D.Int.*1). With the ulnar border of the hand on the table, the fingers extended and the thumb relaxed, the index finger is abducted. Watch for muscle bulk which is obvious on contraction. For resistance—press on the proximal phalanx of the index finger, pushing finger towards adducted position.

Lumbricals 3 *and* 4 (*Lumb.*)—ring and little fingers. With the dorsal surface of the hand upwards and the wrist slightly extended, while keeping the M.P. joints at 90°, the D.I.P. and P.I.P. joints are straightened. Resistance is applied by pressure on the palmar side of each proximal phalanx.

MUSCLES USUALLY SUPPLIED BY MEDIAN NERVE

Pronator teres (*Pro.T.*). With the elbow at 90°, the arm adducted, and the palm facing upwards, the forearm is pronated, i.e., rotated inwards, without moving the elbow, until the palm is facing downwards.

Flexor carpi radialis (F.C.R.) and palmaris longus. With the palm up, the wrist is flexed and the combined strength of the two muscles assessed. Watch for the tendons near to the middle of the front of the wrist. Palmaris longus muscle is sometimes absent.

Flexor digitorum sublimis (*F.D.S.*) to index, *long*, *ring* and little fingers. With the back of the hand on the table, hold down the fingers not being tested. The patient then bends the finger being tested at the P.I.P. joint, keeping M.P. and D.I.P. joints straight. For resistance—press down on the anterior aspect of the middle phalanx. Watch for substitution by the flexor digitorum profundus, by making sure that the D.I.P. joint stays relaxed.

Flexor pollicis longus (*F.P.L.*). The assessor holds the thumb M.P. joint extended and the patient flexes the I.P. joint. For resistance—press upon the distal phalanx of the thumb.

Flexor digitorum profundus (*F.D.P.*) *to the index and long fingers*. See F.D.P. for the ring and little fingers.

Abductor pollicis brevis (*Ab.P.B.*). With the hand on the table, palm up and the thumb on the index finger, the patient abducts the thumb straight up from the index finger and at right angles to the palm. For resistance the assessor presses the thumb straight down towards the index finger.

Opponens pollicis (Opp.P.). The patient abducts the thumb as described for the abductor pollicis brevis, and then brings it across the palm towards the little finger, keeping the thumb I.P. and the M.P. joints extended. Resist in an opposite direction, pressing at the M.P. joint.

Lumbricals 1 *and* 2—the index and long fingers. (See Lumbricals for ring and little fingers.)

MUSCLES SUPPLIED BY THE RADIAL NERVE

Brachio-radialis (*Br.Rad.*). With the elbow at 90°, the arm abducted and the thumb up, the patient flexes the elbow. For resistance—the assessor presses down at the wrist.

Extensor carpi radialis longus and brevis (*E.C.R.L. and B.*). With the hand on the table, pa'm down and the fingers flexed, the patient extends the wrist and deviates it radially. The muscle tendons can be seen together on the radial side of the dorsum of the wrist.

Extensor carpi ulnaris (E.C.U.). Test in a similar way to E.C.R.L. and B., but the wrist is dorsiflexed in ulnar deviation.

Extensor digitorum (*E.D.*). With the fingers extended the M.P. joints are extended. For resistance—the assessor presses down on the proximal phalanges.

Extensor pollicis longus (*E.P.L.*). With the hand resting on the ulnar side of the little finger, the thumb relaxed, the assessor holds the thumb M.P. joint, and the patient extends the distal joint. For resistance—the assessor presses down on the distal phalanx.

V.M.T. TECHNIQUE FOR MUSCLES SUPPLIED BY THE LATERAL POPLITEAL NERVE

Tibialis anterior (*Tib.A.*). With all the toes relaxed or actively flexed, the patient inverts and dorsiflexes the foot. The tendon can be seen and felt. Resist in the opposite direction.

Extensor digitorum longus (*E.D.L.*). Holding the ankle at 90°, the patient extends the lateral 4 toes. The 4 tendons to the toes can be seen and felt. Resist by pressure over the proximal phalanx of each toe in turn.

Extensor hallucis longus (*E.H.L.*). Holding the ankle at 90°, the patient extends the great toe. Resist by pressing against the proximal phalanx.

Peronei (*Per.*). Patient plantarflexes and everts the foot. Tendons of P. longus and brevis can be seen and felt. Resist by pushing against length of 5th metatarsal. These muscles can be tested together but can be distinguished from each other if necessary by watching for depression of the 1st metatarsal which indicates action of the longus muscle.

RESULTS

From November, 1962, to June, 1964, of the 166 Chinese patients with early neuritis all but 2 showed improvement in their serial V.M.T's. In the few patients whose V.M.T's initially showed that some muscles were becoming weaker, it was usually found that the limb was not being rested in a sling; but such an activity as digging in their garden was being indulged in. More extensive drug therapy was instituted and some patients were admitted to hospital bed rest. When nerve pain was uncontrolled by rest and drug therapy, and the V.M.T. showed that some nerve function was still present, operations were performed to relieve pressure on the affected nerve. A few case histories may illustrate the value of V.M.T's:—

1. A.B. Chinese male, 25, hospital number 1590. On admission to the Hong Kong Leprosarium in August, 1963, he was found to have a left low ulnar paralysis, and early median and radial weakness (Table 1).

2. S.K. Chinese female, aged 40, hospital number 1573. Admitted 20th July, 1963, with acute exacerbation of borderline leprosy. She had bilateral ulnar and median weakness and a right drop foot. She was put to bed and cotton wool was bandaged round both elbows, bilateral wrist splints were bandaged on, and a plaster of Paris back slab was made for the right leg to keep the ankle at 90°. Prednisolone was given in a full course. A V.T.M. on the 24th July revealed that there was almost a complete paralysis of the muscles supplied by the right lateral popliteal nerve. However, 6 weeks later the tibialis anterior muscle was strength 4, and the extensor hallucis, extensor digitorum and peronei were half strength (Table 2). On 4th November, 1963, more recovery was found and by 13th February, 1964, all the previously paralysed muscles were at full strength.

3. Mrs. E.F., female, aged 50. In England in November, 1966, this woman with leprosy was found to have a tender right ulnar nerve and both median nerves were tender. She had an established left ulnar paralysis. A V.T.M. was performed which indicated a low ulnar neuritis on the right (Table 3), and bilateral median weakness (Table 4). On the 7th December, 1966, an electrodiagnostic examination was performed by Dr. K. H. Nixon, consultant in physical medicine. The following is taken from his report:—

   (i) *Nerve excitability studies:* These show a decrease in the excitability in the left ulnar nerve.
   (ii) *Motor nerve conduction velocity studies:* These show a delay in the right median nerve of 10 m/secs from wrist to abductor digiti minimi.
   (iii) *Sensory nerve conduction velocity studies:* In the right hand from wrist to little finger there is a good sensory response at 7 m/secs, the upper limit of normal.
   (iv) *I/T Curves:* Partial denervation is demonstrated in the median nerve territory on both sides (Table 5) and in the ulnar nerve territory on the right. There is no denervation in the flexor carpi ulnaris on the right; denervation is in the nerve distal to the nerve origin of this muscle.
   (v) *Electromyography:* This was performed on the abductor pollicis brevis, abductor digiti minimi on the right, and the flexor carpi ulnaris. These show the presence of fibrillation potentials in the abductor pollicis brevis on the right. Interference pattern was complete in the abductor pollicis brevis and reduced in the abductor digiti minimi on the right, and discrete in the second dorsal interosseous on the left.

   Note: If the I/T curves are plotted graphically it can be seen that a greater degree of denervation has occurred on the left than on the right, and the V.T.M's reflect this finding.

   The electromyography needles caused agonising pain to this patient and she was quite unwilling to submit to a second electrodiagnostic examination. However,

TABLE 1

A.B. Chinese male, aged 25. V.M.T. of left hand. August, 1963

Ulnar—(Muscles)		*Median*		*Radial*	
F.C.U.	5	Pro. T.	5	Br. Rad.	5
F.D.P. 3, 4	4, 3	F.C.R.	5	E.C.R.L. and B.	5
A.D.M.	0	Palm L.	5	E.D.	4
O.D.M.	0	F.D.S. 1-4	5554	E.C.U.	5
D. Int. fig. I.	0	F.P.L.	5	E.P.L.	4
Lumb. 3 and 4	0, 0	F.D.P. 1, 2	5, 5		
		Ab.P.B.	4		
		Opp.P.	5		
		Lumb. 1, 2	3, 2		

TABLE 2

S.K. Chinese female, aged 40. Right foot V.M.T.

	24.7.63	3.9.63	4.11.63	13.2.64
Tibialis anterior	0	4	5	5
Extensor hallucis	0	2	3	5
Extensor digitorum	1	3	4	5
Peronei		3	5	5
Passive dorsiflexion	75°	70°	70°	70°
Active dorsiflexion	105°	87°	80°	80°

TABLE 3

Mrs. E.F., aged 50. Right hand. V.M.T's ulnar-supplied muscles

	14.12.66	8.2.67	19.4.67
F.C.U.	4	5	5
F.D.P.	4	4	5
A.D.M.	4	4	4
D.Int.I.	3	4	4
Lumb. 3, 4	4	4	5

TABLE 4

Mrs. E.F. V.M.T's of median supplied muscles—left is weaker than right

RIGHT			*LEFT*	
19.4.67	14.12.66		14.12.66	19.4.67
5	5	Pro.T.	4	4
5	4	F.C.R.	4	4
5	5	F.D.S., 1-4	5	5
4	4	F.D.P. 1, 2	4	4
5	4	An.P.B.	3	3
5	4	Opp.P.	4	4
5	4	Lumb. 1, 2	4	4

TABLE 5

Mrs. E. F. Part of electrodiagnostic examination. December, 1966

I/T Curves		*Right*	*Left*
Abductor pollicis brevis	100 m/s		75
	30 m/s	1	8
	10 m/s	1.3	1.6
	3 m/s	2.3	5.0
	1 m/s	4.1	6.0

TABLE 6

T.A. Ethiopian male, aged 18. Serial V.M.T's of ulnar-supplied muscles

RIGHT		*LEFT*				
8.11.67		8.11.67	3.1.68	21.2.68	4.4.68	7.5.68
5	F.C.U.	5	5	5	5	5
5555	F.D.P.	5554	5554	5554	4545	4545
5	A.D.M.	3	3	5	3	5
5	O.D.M.	0	2	5	3	4
5	D.Int.1	3	4	4	5	5
5	2	0	3	4	5	5
5	3	0	2	2	4	5
5	4	0	2	2	3	4
5	Lumb. 4	0	2	2	2	3
5	3	2	2	3	3	3

she was taught hand exercises for her weak muscles, given a sling for the right arm and appropriate drug treatment. Serial V.T.M's were performed and showed recovery of muscle strength after 4 months (Tables, 3 and 4).

4. T.A. Ethiopian male, aged 18. This young man was seen in November, 1967, when his B.I. was 0.0, after he had been treated for 2 years for borderline leprosy. He complained of pain in his ulnar nerves which were found to be grossly enlarged and tender, and the left hand had demonstrable ulnar weakness. A V.T.M. showed that the right hand ulnar-supplied muscles were normal strength, while the left hand had a low ulnar neuritis with marked weakness of most of the short muscles of the hand (Table 6). He was admitted to hospital and treated with a full course of Prednisolone. A V.T.M. on 3rd January, 1968, showed recovery in nearly all the muscles, with more improvement by the 21st February. He was then treated as an out-patient, but in April he complained again of acute nerve pain and a V.T.M. showed that there was slight weakness of some muscles which had been at normal strength in February (Table 6). This was regarded as an indication for hospital admission, and he was also treated with Prednisolone again. AV.T.M. on the 7th May, 1968, showed recovery of strength, and presumably of nerve function in nearly all the muscles. He was discharged again for out-patient treatment.

DISCUSSION

To assess the presence and extent of nerve damage in leprosy neuritis it has been shown that the Voluntary Muscle Test (V.M.T.) is extremely valuable. It is doubtful whether complex electrodiagnostic studies add much useful information to that obtained by a V.M.T. except in very early neuritis. Inasmuch as a V.M.T. of the muscles in one hand relevant to reveal neuritis can be efficiently performed in 5 or 10 minutes and involves no equipment, it is suggested that, for the time required, this test provides a greater amount of information than can be acquired by any other test; and should be recorded for every patient found to have early neuritis. Sensory testing requires a much greater length of time for one test, and serial sensory tests require many record sheets, in contrast to the V.M.T. which is recorded in parallel columns; and with the latter test improvement or worsening can be seen at a glance. A comparison of V.M.T. results and the stage at which protective sensation is retained in the hand will be the subject of a further paper. However, it can be stated that among Chinese patients, and in the few Ethiopian patients so far studied, definite weakness of the short muscles of the hand occurs in most patients before loss of *protective* sensation. Thus the V.M.T. can be used not only to recognise the stage at which normal hand movements can be saved, but also the stage at which protective sensation probably can be saved; and as such can be seen to be of double value.

Mendis (1965) in his booklet on physiotherapy in leprosy devotes a very small paragraph to the problem of neuritis. He advocates the use of electrical assessments, namely 'intensity-duration graphs', and mentions that 'these graphs detect minor degrees of denervation that may escape a clinical assessment'. However, the equipment and skill required for successfully making these electrical graphs are rarely found in leprosy centres and the time required renders them impracticable in circumstances where large numbers of leprosy patients are being treated and the great majority of patients with early neuritis are being detected. The Manual muscle test has been used by Furness (1967) to assess function during treatment for recent paralysis in leprosy patients, and at the National Institute of Allergy and Infectious Diseases in Maryland (Atkinson *et al.*, 1967). The M.R.C. muscle tests (Report, 1943) are also used by Parry (1958).

In the 'Manual for training leprosy rehabilitation workers' (Itch and Eason, undated), the strength of muscles is classified as 'functional' or 'non-functional'. However, small degrees of improvement or regression are difficult to assess when these 2 grades alone are used, and this classification would divorce leprosy physiotherapy from the main-stream of physiotherapy in the world.

Harris (1964) has pointed out that claims for the successful treatment of leprosy neuritis have been worded extremely vaguely, 'excellent', 'beneficial', 'successful'. He recommends that many sensory tests should be performed, including the ninhydrin test for sweating. He couples these delicate tests with observations which would appear to be less delicate, such as wasting, and the patient's type of grasp, whether

the fingertips dig into the forearm of the examiner; but both of these tests are difficult to record objectively. He describes measurement of the strength of pinch and grasp with a 'pinchometer' and a 'dynamometer'. The dynamometer is composed of a rubber bulb and an air pressure gauge filled with hydraulic oil and then air. However, in leprosy hospitals in developing countries this instrument can easily become damaged and inefficient (Ward, D. J., personal communication).

The 'fatigue' test for early ulnar paralysis is obviously of great value (Harris, 1964), but if very delicate tests are used routinely, treatment must be instituted correspondingly early and the number of patients under treatment will be vastly increased, probably beyond the bounds of possibility that one unit could manage at any one time. Furthermore the patient may be unco-operative under treatment if he does not feel that his hand is abnormal. Harris acknowledges that some degree of spontaneous recovery occurs in many forms of neuritis, and thus it would be reasonable to treat as a first priority patients whose neuritis is more than minimal.

Watson (1965) has described her opinion of the V.M.T. She states that she has found the V.M.T. 'completely satisfactory for routine testing, and would recommend it for use in most institutions. The tests can be taught to most technicians who have learned the positions of the muscles of the hand and forearm. They do need to be carefully taught; and accuracy is acquired only by care, by practice, and by knowledge of trick movements to be avoided. My 3 patient assistants, none of whom have completed their 'middle-school' education, have all learned the position of the hand muscles, by way of diagrams and explanations, and are all doing voluntary muscle tests routinely.'

SUMMARY

The Voluntary Muscle Test (V.M.T.) is a rapid, reliable and reproducible assessment of the extent of nerve damage in leprosy neuritis, and requires no equipment. Definite muscle weakness is revealed in hands that appear normal to a casual observer, and in such patients active treatment for neuritis is immediately indicated. The results of treatment can be objectively judged by serial V.M.T's, and when V.M.T's are recorded in parallel columns they can be rapidly compared. For speed, interpretation and comparability V.M.T's are superior to sensory tests. As a guide to the treatment of patients in developing countries, electrical studies probably do not add much vital injormation to that obtained by a V.M.T. Restoration of nerve function and muscle strength as shown by serial V.M.T's may frequently be accompanied by a preservation of protective sensation in the hand. The technique of doing a V.M.T. can be readily taught to nurses and physiotherapy auxiliaries, and has been found to be invaluable and entirely satisfactory in Chinese, English and Ethiopian leprosy patients.

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Treatment of Ulnar Neuritis and early Ulnar Paralysis

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In the last 2 decades, reconstructive surgery for the deformities associated with leprosy has come into its own. However, surgery can rarely restore full range of movement or bring back lost sensation. In spite of sulphones and other anti-leprosy drugs, neuritis sometimes supervenes, with resulting deformities and trophic ulceration.

Many workers have tried to relieve the pain of ulnar neuritis with drugs, and others have attempted different surgical procedures with the same intention. Various operative techniques are described such as: external neurolysis, neurolysis combined with longitudinal incision of the epineurium, endoneurolysis and fascicular neurolysis.

Most of the serious disabilities occurring in leprosy are the consequence of damage to mixed nerve trunks. Such damage is usually associated with swelling of the nerve, and secondary ischaemia may be the immediate factor causing damage by compression.

The surgical procedure of choice at the Leprosy Centre, Polambakkam, is external neurolysis. The patients were selected at random. Those with bilateral neuritis (mostly acute), those whose nerves were less enlarged or with hands with slight degrees of paresis or paralysis were kept as controls, as were also some others with unilateral neuritis.

Full records were kept of duration of pain, sensory charting (with nylon No. 5), motor power of muscles, and the patients' own statements concerning ability to work; all these were noted before and after treatment.

The operative technique was as follows (Figs. 1 to 3): An incision of about 3 inches was made over the ulnar groove. After dissection of the superficial tissues, the ulnar nerve was identified and its fascial roof divided. The dissection was continued distally to the point where the nerve dips between the 2 heads of the flexor carpi ulnaris. The fibrous arch was divided completely, and then excised in order to prevent further adhesions. No tourniquet was used, and care was taken not to infiltrate the nerve or to incise its sheath. The following observations were made at operation: The nerves were enlarged proximal to the arch and compressed at the arch itself. The arch was thickened. The nerve was white proximally, but distal to the arch it was yellowish. Shortly after decompression, the vasa nervorum on the antero-lateral aspect of the nerve could be seen filling up. The patient volunteered that he experienced relief of pain soon after division of the fibrous arch.

After the operation, the paralysed hands were immobilised in the lumbrical position for 3 to 4 weeks. After the removal of plaster, massage and exercise of the hands were encouraged. Tables 1 and 2 give the analysis of the treatment and control groups.

RESULTS

Neuritis (Table 3). Forty patients in whom the nerve was compressed after a short period of fibrous constriction, had no recurrence; out of 45 patients in whom the constriction was of long duration, 43 had no recurrence. Table 4 gives the corresponding results for the controls.

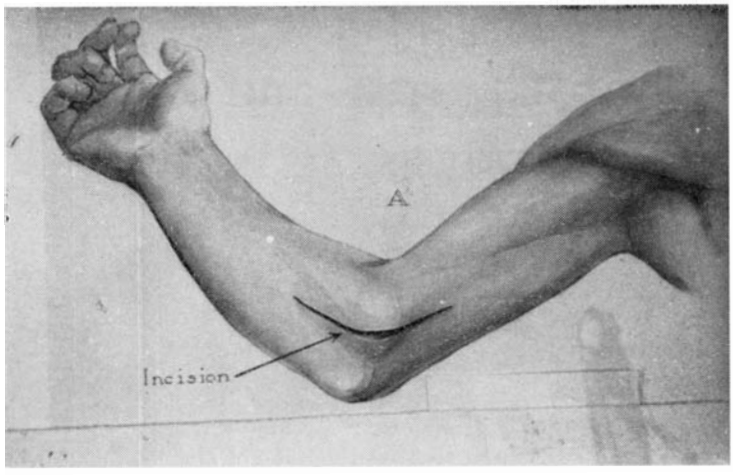

Fig. 1

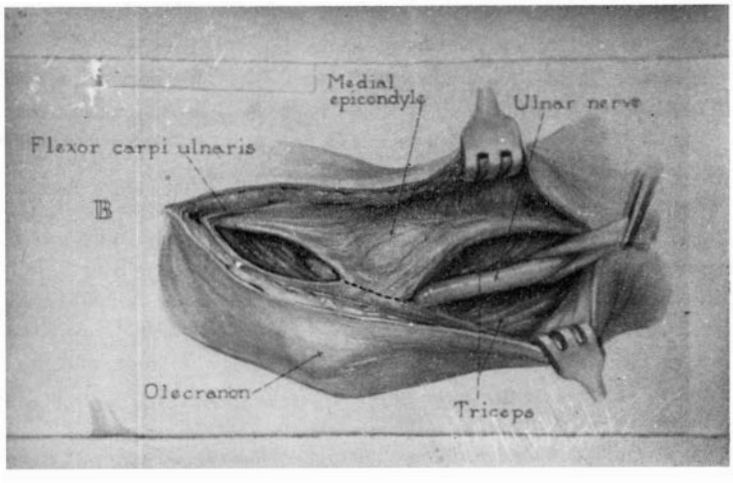

Fig. 2

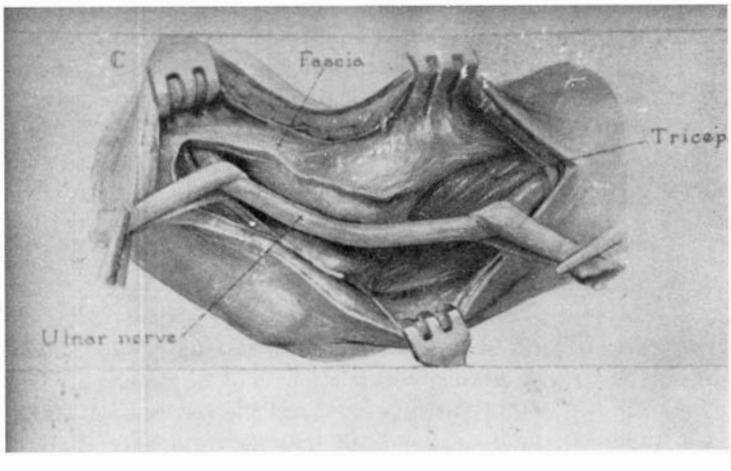

Fig. 3

TABLE 1

Analysis of 88 patients undergoing decompression of nerve

Type	*LEFT HAND*			*RIGHT HAND*		
	Male	*Female*	*Total*	*Male*	*Female*	*Total*
Lepromatous	13	2	15	16	5	21
Tuberculoid	16	1	17	12	5	17
Borderline	5		5	4	—	4
Polyneuritic	2		2	5	2	7
Total	36	3	39	37	12	49

TABLE 2

Analysis of 24 control patients

Type	*LEFT HAND*			*RIGHT HAND*		
	Male	*Female*	*Total*	*Male*	*Female*	*Total*
Lepromatous	8	3	11	7		8
Tuberculoid	2		2	1		
Borderline ..			1	1		
Polyneuritic						
Total	11	3	14	9		10

TABLE 3

Analysis of 85 patients with neuritis after decompression

Type	*SHORT DURATION (Within 3 months)*					*LONG DURATION (Above 3 months)*				
	Non-recurrence of Neuritis		*Recurrence of Neuritis*		*Total*	*Non-recurrence of Neuritis*		*Recurrence of Neuritis*		*Total*
	No.	*%*	*No.*	*%*	*No.*	*No.*	*%*	*No.*	*%*	*No.*
Lepromatous	17	94.4		5.6	18	15	83.3	2	11.7	17
Tuberculoid	17	100	—	—	17	17	100	—		17
Borderline	2	100	—	—	2	5	100	—	—	5
Polyneuritic	3	100	—	—	3	6	100	—	—	6
Total	39	97.5	1	2.5	40	43	95.6	2	4.4	45

TABLE 4

Analysis of 24 control patients with neuritis

Type	*SHORT DURATION (Within 3 months)*					*LONG DURATION (Above 3 months)*				
	Non-recurrence of Neuritis		*Recurrence of Neuritis*		*Total*	*Non-recurrence of Neuritis*		*Recurrence of Neuritis*		*Total*
	No.	*%*	*No.*	*%*	*No.*	*No.*	*%*	*No.*	*%*	*No.*
Lepromatous	2	28.6	5	71.4	7	3	25	9	75	12
Tuberculoid								3	100	3
Borderline		100			1			1	100	1
Polyneuritic										
Total	3	37.5	5	62.5	8	3	18.75	13	81.25	16

TABLE 5
Analysis of 85 patients with sensory loss after decompression

Type	SHORT DURATION (Within 3 months)							LONG DURATION (Above 3 months)						
	Sensory Recovered		Sensory Stationary		Sensory Worsened		Total	Sensory Recovered		Sensory Stationary		Sensory Worsened		Total
	No.	%	No.	%	No.	%	No.	No.	%	No.	%	No.	%	No.
Lepromatous	11	61	6	33.3	1	5.7	18	3	17.6	14	82.4			17
Tuberculoid	8	47	9	53	—	—	17	2	11.7	15	88.3			17
Borderline	—	—	2	100	—	—	2	—	—	5	100			5
Polyneuritic	1	33.3	2	66.7	—	—	3	2	33.3	4	66.7			6
Total	20	50	19	47.5		2.5	40	7	14.4	38	85.6			45

TABLE 6
Analysis of 24 control patients with sensory loss

Type	SHORT DURATION (Within 3 months)							LONG DURATION (Above 3 months)						
	Sensory Recovered		Sensory Stationary		Sensory Worsened		Total	Sensory Recovered		Sensory Stationary		Sensory Worsened		Total
	No.	%	No.	%	No.	%	No.	No.	%	No.	%	No.	%	No.
Lepromatous	2	28.6	4	57.2	1	14.3	7	—	—	10	83.3	2	16.7	12
Tuberculoid	—	—	—	—	—	—	—	—	—	3	100	—	—	3
Borderline	—	—	—	100	—	—	1	—	—	1	100	—	—	1
Polyneuritic	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Total	2	25	5	62.5	1	12.5	8	—	—	14	87.5	2	12.5	16

TABLE 7
Analysis of patients with paralysis after decompression

Type	SHORT DURATION (Within 3 months)							LONG DURATION (Above 3 months)						
	Recovered Completely		Stationary		Worsened		Total	Recovered Completely		Stationary		Worsened		Total
	No.	%	No.	%	No.	%	No.	No.	%	No.	%	No.	%	No.
Lepromatous	5	71.43	2	28.57	—	—	7	4	36.36	7	63.64	—	—	11
Tuberculoid	7	63.64	4	36.36	—	—	11	1	7.14	13	92.86	—	—	14
Borderline	1	100	—	—	—	—	1	1	14.3	6	85.7	—	—	7
Polyneuritic	2	100	—		—	—	2	—	—	4	100	—	—	4
Total	15	71.43	6	38.57	—	—	21	6	16.7	30	83.3	—	—	36

TABLE 8
Analysis of 12 control patients

Type	SHORT DURATION (Within 3 months)							LONG DURATION (Above 3 months)						
	Recovered Completely		Stationary		Worsened		Total	Recovered Completely		Stationary		Worsened		Total
	No.	%	No.	%	No.	%	No.	No.	%	No.	%	No.	%	No.
Lepromatous		100							14.3	5	71.4		14.3	7
Tuberculoid										3	100			3
Borderline				100										
Polyneuritic														
Total		50		50			2		10	8	80		10	10

Sensory Changes (Table 5). In the first group of 40 patients, 20 had complete recovery of sensation, and in the second group of 45, only 7 recovered sensation. Table 6 gives the results for the controls. Decompression thus helps in preventing further episodes of neuritis and damage to the nerves.

Paralysis (Table 7). Of 21 patients with paralysis of the hands of short duration, 15 recovered completely after decompression and 6 remained stationary; of 36 who had paralysis of long duration, only 6 recovered completely and 30 remained stationary. Table 8 gives the results for the controls.

DISCUSSION AND CONCLUSIONS

From the observations recorded, we agree with Chatterjee (1955) that the neural signs and symptoms of leprosy have a close relationship with the blood supply to the nerves.

SUMMARY

Relief of pressure on the ulnar nerve by operative section of the constricting fibrous arch just above the heads of origin of the flexor carpi ulnaris is held to account for the good clinical results in 85 patients. Motor paralysis of short duration showed complete recovering, and sensation returned in a smaller proportion of patients.

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Leprosy in Society
IV. The Genesis of Lepra-Angst*

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The term 'Leprofilia' (Leprophilia) has been proposed[1] to designate the phenomenon of the wish to have or be thought to have, leprosy, shown especially by some wives of leprosy patients who try to prove that they have this disease primarily so that they can remain with their segregated husbands. The self-explanatory term 'Leprophobia' is commonly used to indicate fear of leprosy. In this paper, the term 'Lepra-angst' will be employed to cover the various emotions shown by individuals who, not having leprosy, believe themselves to be so afflicted, and are disturbed by the possibility.

Experience in those medical clinics in Hong Kong which are devoted exclusively to the treatment of leprosy often leaves the observer impressed with the evident diagnostic acumen of medically illiterate peasants and common people with respect to leprosy. It is uncommon, if not rare, to have patients show up at these specialty clinics if they do not have leprosy and if other medical facilities are available to them. It is therefore remarkable, when under these circumstances, occasional persons appear at the clinics who have no evidence of leprosy but who display an agitated conviction that they are so afflicted. Enough such instances were encountered to excite curiosity and investigation as to the underlying reason for this anxiety.

THE DATA

Twenty-three patients, 2 female and 21 male, displaying lepra-angst appeared in leprosy clinics over a total period of 6 months observation. In age, they ranged from 21 to 50 years.

These patients were each interviewed on one occasion only. The interview was conducted in their own language, in a relaxed, friendly atmosphere with the interview often lasting up to 2 hours. Their concepts and tales concerning leprosy were sought and in the process their reasons for believing that they had leprosy gently probed. Subsequently these beliefs were discussed with them in the light of medical knowledge of this disease and, after careful examination had revealed no evidence of leprosy, they were assured that they did not have this disease. No follow-up was possible, but, as far as is known, none of the patients returned to this specialty clinic. None of the patients revealed any disease lesions other than small furuncles or similar minor blemishes.

The interviews were conducted against a background tapestry of information provided by a prior, extensive study of folklore and beliefs relating to leprosy[3 4 5] as held by this same ethnic group

Pertinent data for each patient are summarised in Table 1.

INTERVIEWEES' CONCEPTS OF LEPROSY

The concepts of leprosy held by these patients in general paralleled those previously noted[2] in a study of the folklore and beliefs relating to leprosy in the population of South China. Among these, the following were repeatedly reiterated and are therefore listed as contributory to an understanding of the lepra-angst.

* This study was initiated under a leprosy research and development grant from American Leprosy Missions Inc. and completed in association with studies under NIH Grant AI-03627.

TABLE 1

Patient basis for Lepra-angst

	Patient	*Age*	*Sex*	*Marital status*	*Occupation*	*Pertinent Observations*
1.	P.T.	39	M	Married	Labourer	One year previously called on a prostitute and as a result developed a feeling of 'insects crawling under the skin'. Symptoms continued despite treatment, so became convinced he had leprosy.
2.	K.M.	34	M	Widower	Office boy	Coitus 3 months previously with prostitute. Three weeks later developed feeling of 'insects crawling around in the body.' Feared contracting leprosy as a result of his prostitute contact.
3.	C.S.	28	M	Married	Broker	Had intercourse 3 months previously with prostitute and 3 weeks later noted a skin eruption. Physician diagnosed syphilis, treated same and pronounced patient cured. Patient believed leprosy was contracted predominantly by prostitute contact, that his health was not fully normal, and that he probably had leprosy.
4.	L.T.M.	25	M	Married	Meat dealer	Relations with a prostitute 5 months previously and believed that the usual way to contact leprosy was through such contact.
5.	Y.C.	24	M	Single	Labourer	Two years previously developed penile lesions after relations with some prostitutes. Self-treated with penicillin ointment. One year later developed a series of pustules and presently was under treatment with sulfathiazole. Believe leprosy contracted through coitus with prostitutes having leprosy.
6.	L.M.	26	M	Single	Tailor	Three years previously contracted venereal disease after intercourse with some prostitutes; treated in Social Hygiene Clinics. Five months previously again visited a prostitute and noted inguinal lymphadenopathy. Treated but believed he still was ill and that he had leprosy. Believed leprosy transmitted mainly by intercourse with 'bad girls'.
7.	H.K.	39	M	Married	Merchant	One year previously he spent a night with a prostitute and subsequently developed a strong fear that he would develop leprosy.
8.	C.C.C.	40	M	Married	Private tutor	Would not admit extra-marital coitus. Declared strong sexual interest in wife but noted that for 4 months he had a fear of ejaculating during relations with her. Highly agitated and fearful. Believed leprosy was transmitted by sexual intercourse. Recognised a general belief that people with leprosy were guilty of moral misconduct.
9.	C.M.Y.	50	M	Married	Labourer	Spent a night with a prostitute about one month previously. Subsequently believed that there was slight swelling of ears and face and that he had contracted leprosy from this incident.
10.	W.C.Y.	26	M	Married	Merchant	About 6 months previously the patient had related with some prostitutes and subsequently noted itching of the face and some dizziness. Believing that those who had bed contact with 'bad girls' were most likely to contract leprosy, he had this fear.

TABLE 1

	Patient	*Age*	*Sex*	*Marital status*	*Occupation*	*Pertinent Observations*
11.	L.C.	43	M	Married	Coolie	During sexual congress with a prostitute 4 years previously, some blood escaped from the woman's vagina and he feared he might get 'some disease'. The following year he noted a small boil on his left eye and went to a V.D. clinic for treatment. During the past year he felt 'itching' on the face and thought that his face had reddened and his nose thickened and he believed that he had leprosy.
12.	C.L.	42	M	Married	Medicine dealer	Previous venereal disease. Ten months previously he had visited his wife in another city for a few days. On returning to Hong Kong he noted itching of his face. At about this time he chanced to read the advertisement of Wang Kuang Fa* and developed an overwhelming fear that he had leprosy. Emphasised that leprosy is contracted by sexual intercourse.
13.	T.G.B.	37	M	Married	Coolie	Prostitute relationships several times in past year. Twenty days after the last he was treated for gonorrhea successfully. However, he noted 'itching like ants crawling under the skin' and feared that he had leprosy. This suspicion strengthened by the advertisement of Wang Kuang Fa*. Believed that leprosy caused by relations with prostitutes.
14.	C.C.W.	24	M	Single	Private tutor	Denied sexual congress. One month previously noted some of his eyebrow hairs falling in basin when washing face. Later found some vesicles on his palms associated with 'itching'. Concomitantly he chanced to read the advertisement of Wang Kuang Fa* and concluded that he had leprosy. Convinced that leprosy was transmitted by sexual intercourse.
15.	N.K.	36	M	Single	Carpenter	One year previously he spent a whole night with a prostitute and subsequently began to have persistent 'itching' on face and feet which continued despite visits to many doctors. Extremely anxious and uncommunicative save for fear that he had leprosy.
16.	L.M.	32	M	Single	Labourer	Venereal disease history and had 'itching of face' for past year. The latter persisted despite treatment at V.D. clinic. Saw advertisement in newspaper* which suggested that such itching of the face was a sign of leprosy. Believed he had leprosy. Also believed leprosy to result from immoral sexual behavior.
17.	C.P.	40	M	Married	Labourer	Ten months previously he visited a prostitute, which behaviour he considered very immoral and following which he began to note generalised 'itching' and sometimes some small red spots in his skin. Also had feeling of 'ants crawling in his body, especially about the anus'. Became impotent. Treated in V.D. clinic without improvement of these symptoms and believed he was developing leprosy.
18.	L.C.	36	M	Single	Unemployed	Ten years previously had positive Wasserman and Kahn tests and was treated for syphilis. Since then had served prison terms and hard labour sentences for political reasons. Two years ago noted 'itching on face and alopecia and feared he was contracting leprosy'. Did not acknowledge sexual contact but believed leprosy to be transmitted by such contact.

* See Fig. 1 for reproduction and translation of advertisement.

TABLE 1

	Patient	*Age*	*Sex*	*Marital status*	*Occupation*	*Pertinent Observations*
19.	L.Y.S.	38	M	Single		Three years previously the patient visited a prostitute several times and developed gonorrhea for which he was treated. Stated: 'Because I made several coitus with bad girls, I am afraid of getting such terrific disease (leprosy)'.
20.	T.Y.S.	28	M	Married		Patient had his second relation with a prostitute 4 months previously and contracted syphilis. Though treated for this, he soon began to itch in his ears and then generally, with a sensation as of insects or ants crawling within his skin. As a result he developed a very nervous state, believing that he had contracted leprosy.
21.	C.K.	27	M	Married	Coolie	Patient had veneral disease 8 years previously and subsequently he began to think that his eyebrows seemed to fall out easily on washing. He thought this due to syphilis but when he lately developed 'itching' inside his body he concluded that he also had leprosy. He believed that if syphilis was not cured quickly leprosy would result.
22.	Y.O.	37	F	Married	Labourer	She had intercourse with her husband during menstruation and thought that this 'dirty sexual behaviour' might cause leprosy.
23.	T.Y.P.	21	F	Single	Student	A very attractive young lady who blandly denied any sexual relationships and blamed some vague contact with leprosy 8 years previously for her present lepra-angst.

1. The major means of contracting leprosy for males is through sexual relations with prostitutes or through abnormal human sexual relationships.
2. Leprosy is also a congenitally transmissible disease. Some patients indicated a belief that leprosy so transmitted would not reveal itself until recipient reached adulthood, married and had sexual intercourse. It would then become manifest.
3. Leprosy is incurable and there are no gods that will grant its cure.
4. If a person having leprosy can have sexual relations with a healthy individual he will, by transmitting a portion of his disease, reduce his own infection. Amelioration only, and not cure, can be thus achieved. The practice is attributed to leprous persons of either sex and is termed 'selling leprosy'.
5. Leprosy can be caused to be concentrated in less visible portions of the body by various means such as eating small granules or ashes of silver or through consuming human placenta.
6. Persons contracting leprosy are generally 'bad' persons, having contracted it by immoral behaviour and being suspect of wishing to 'sell' it to others. The appearance of leprosy is therefore certain to cause loss of position and disgrace as well as ostracism.
7. Signs of lepsory are: enlargement of both ears, nodules on the face, loss of eyebrows, extremity deformity such as claw hands, facial and body 'itching' and a sensation as of insects crawling under the skin.

DISCUSSION

Ryrie[2], writing on the psychology of leprosy, noted that in 3 major categories of persons associated with leprosy—one of which was the patient group—there is a single common factor, namely, irrational fear. He stated, 'It must be made clear from the start that this irrational fear

Fig. 1a
Newspaper advertisement of herbalist Wang Kuang Fa.

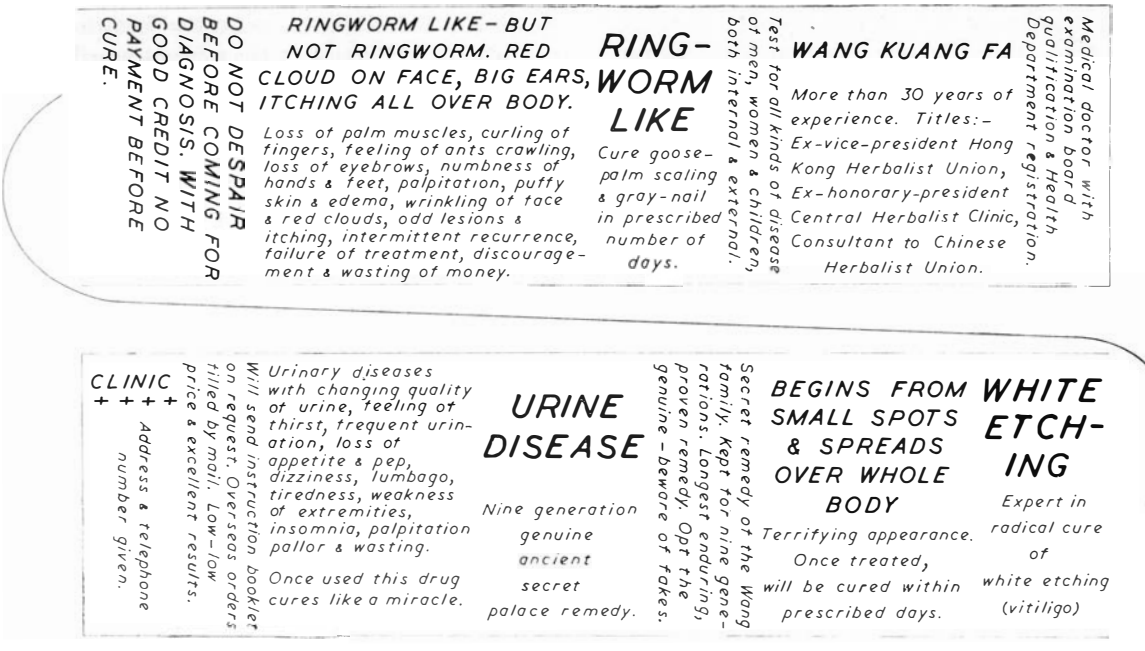

Fig. 1b
Translation of above advertisement. Reads from right to left.

is activated by the inherent sense of guilt which is part of the psychological inheritance of man.' He pointed to an almost universal tendency to regard leprosy as being dirty, all-infectious, cruel and venereal. Further, 'The most immediate and marked effect of the psychology of the leprosy patient is the overwhelming sense of shame and disgust, which again springs from the guilt-punishment-complex.'

The data available from this limited group of patients is so overwhelmingly similar in nearly each instance, and so compatible with previously determined social concepts of leprosy held by this ethnic group, as to suggest that the following conclusions are tenable:—

1. In the ethnic group considered, the dominant basis for lepra-angst is concern over retributive consequences of sexual

misconduct. A strong theme of fear and guilt is found in the patients concerned and is supported by an almost compulsive need on the part of many of them to express the concept that people with leprosy are bad people who have been 'bad' sexually. The age group in which lepra-angst appeared is compatible with this conclusion as is also the preponderance of males.

2. Related to this is the fear of retributive consequences of the breaking of sexual taboos, e.g., coitus during menstruation, as demonstrated by Patient No. 22.
3. Personal, relatively casual contact with persons having leprosy is not a major factor in the development of lepra-angst.

The population of Hong Kong is only partially indigenous, there having been an increase of striking magnitude since 1948 due to refugee immigrants. Excluding this increment, a considerable portion of which came from North and Central China, the majority of the inhabitants are from South China. Though they live in Hong Kong, they maintain close connections with their home districts and reflect the customs and beliefs of these areas. When asked where their home is they will almost invariably indicate their district of origin as 'home'. All the patients, save No. 23, in this survey were from the contiguous province of Kwangtung and represented 18 districts of this province, there being 4 districts each of which was represented by 2 patients. Patient No. 23 was a visitor in Hong Kong from Taiwan (Formosa).

For 4 patients an apparent precipitating factor in resolving their guilt feelings into lepra-angst was the newspaper advertisement of herbalist Wang, reproduced with translation as Fig. 1. It is of interest that the advertisement does not use any specific name to identify its section referring to leprosy. It does list for this disease a greater number of signs and symptoms than for the other diseases identified. Despite the lack of name identification, none of the 4 patients had any doubt but that the advertisement referred to leprosy. It may be assumed that the list of signs and symptoms given by this experienced herbalist are those most commonly used, in this population area, to identify leprosy. The practice followed in this advertisement, which was clearly designed to attract patients by playing on their fears, suggests that in a population where leprosy is endemic it is the disease entity itself, and not the name for the disease, which carries the basic rationale for social opprobrium toward its victims[5]. In all probability, any name which identifies this disease complex will call forth such opprobrium.

Much of the fear attendant on leprosy is related to misconceptions, such as those here identified as significant in the genesis of lepra-angst. The greatest strides in overcoming society's lepra-opprobrium can be expected from extended publicity designed to dispel such misconceptions and to relate the known facts concerning the disease to the present possibilites of prevention, cure and rehabilitation. Individual members of society, as witness the ready response of the patients reassured in this study—referring only to their retributive association of leprosy with their guilt complex and not to any possible resolution of the guilt feeling itself—often respond readily to such information.

SUMMARY

Lepra-angst is identified as the guilt-fear of individuals who, not having leprosy, believe themselves to be so afflicted. Twenty-three patients, troubled by this anxiety were interviewed and the findings identify the source of their fear complex as a fear of retributive consequences of sexual peccancy. The genesis of lepra-angst in this ethnic group is correlated with prior studies of the folklore and concepts of leprosy prevalent in South China.

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Abstracts

1. Leprosy in Kenya, by M. Ziedses des Plantes, A. R. H. B. Verhagen, D. Leiker and J. W. Koten. *East African Medical Journal*, **45**, 6, June, 1968.

The absence of reliable vital statistics is nowhere more obvious and more serious than in the assessment of the prevalence of leprosy and the planning of measures for successful control. This report indicates that in Kenya leprosy is more common than was formerly believed, and is present in hitherto unsuspected foci. Suggestive pointers were first noted during an analysis of the tribal and geographical origins of leprosy patients in an urban clinic. These suspicions were confirmed by sample and pilot surveys, by 'whole-population' surveys, admittedly incomplete, and by more thorough investigation of supposedly hyperendemic foci.

The obvious lessons to be learned from this study are that there are always more patients suffering from leprosy than early reports suggest; that the provision of inadequate facilities for in-patient treatment of a proportion of patients with multibacillary disease has little or no effect on the prevalence of leprosy; that control measures beset with such shortcomings as incomplete coverage with treatment centres, delay in reporting for treatment, high defaulter rate, and absen follow-up of defaulters—are scarcely able to contain the leprosy endemic. Movements of people from country to town, and within the rural areas, coupled with a natural increase in the numbers exposed to leprosy, also increase the possibility of leprosy infection.

S. G. Browne.

The following 7 abstracts are reprinted, with permission from *Trop. Dis. Bull.*, 1968, **65**, 5:

2. **Leprosy in New Brunswick: the end of an era,** by F. L. Whitehead *Can. Med. Ass. J.*, 1967, **97**, 21, 1299-300.

Leprosy entered New Brunswick in 1815, attacked about 320 people, and quietly disappeared in 1965. Apparently, the 3 first victims were sisters, of French extraction, but their 16 sibs and half-sibs were unaffected. Where they contracted the disease is a mystery, never to be solved. This account of a small and limited outbreak of leprosy traces briefly the history of the earliest lazaretto on Sheldrake Island, with its 18 inmates in 1844, and the lazaretto in Tracadie, which was a 'cheerless prison, surrounded by a wall 12 feet high, with a row of long spikes on the top to prevent escape'. In those days, 'lepers' (*sic*) 'were hunted like wild beasts, dragged from their lairs by an iron hook attached to a long pole, handcuffed'. A better day dawned with a new attitude to leprosy sufferers, and new hope came 20 years ago with the sulphones. The last 2 patients from New Brunswick itself were admitted in 1937, though a few patients from other provinces came to Tracadie during the next 15 years. The last patient was discharged in 1965.

In an accompanying editorial (p. 1298) Aequanimitas pays tribute to the succession of dedicated workers whose efforts have brought the era of leprosy in New Brunswick to an end.

(No valid epidemiological conclusions can be drawn from this interesting conspectus concerning the value of segregation as a means of controlling a limited outbreak of leprosy in a developed country.)

S. G. Browne.

3. **Leprosy. II. IgA and IgM immunoproteins in leprosy sera,** by S. D. Lim and R. M. Fusaro *Int. J. Lepr.*, 1967, **35**, 3, 355-60. **III. A comparison of IgA and IgM immunoproteins of patients with pulmonary tuberculosis and leprosy,** by S. D. Lim and R. M. Fusaro. *Ibid.*, 361-5.

II. Reports on immunoelectrophoretic changes in IgA and IgM immunoglobulin in 15 leprosy patients were previously recorded (*Trop. Dis. Bull.*, 1964, **61**, 574). This report summarises the serum protein changes in 232 leprosy patients studied by the same methods. Serum electrophoresis was carried out in agar gel on slides and anti-human serum was prepared in horses. Control sera from normal subjects were examined at the same times as those from leprosy patients. Results indicated that IgA globulins were most active in tuberculoid leprosy (91%) and least active in the lepromatous type (51%). IgM globulins occurred in 99% of patients with lepromatous leprosy, in 62% with the tuberculoid type and in 49% of indeterminate type.

III. The authors have now compared their findings in tuberculous and leprosy patients. In 50 patients the diagnosis of tuberculosis was established by clinical and laboratory studies. 25 sera from normal patients were compared. The results obtained by electrophoresis in these 2 groups of patients are tabulated. In the tuberculous patients the changes in IgA were more numerous than in the IgM fraction of serum. The findings were closely comparable to those occurring in the sera of patients with tuberculoid leprosy but differed from those with lepromatous leprosy.

J. D. Fulton.

4. **A logarithmic index of bacilli in biopsies. 1. Method,** by D. S. Ridley and G. R. F. Hilson. *Int. J. Lepr.*, 1967, **35**, 2, Pt. 1, 184-6. **2. Evaluation,** by D. S. Ridley. *Ibid.*, 187-93.

1. The usual method of assessing the state of the disease in patients with leprosy, both before and during treatment, is based on the number of bacilli present in smears, i.e., the bacterial index. However, Ridley (*Trop. Dis. Bull.*, 1956, **53**, 200) suggested that this method ignores the extent of the granuloma and its diminution during treatment. He therefore suggested that the biopsy index (IB) is more informative because it is based on the extent of the granuloma as seen in

sections and the number of bacilli in smears. However, in the first of these papers, the authors now suggest that the IB is also unsatisfactory because its calculation involves an arithmetical component and a logarithmic component; they therefore suggest the adoption of a logarithmic scale for both components.

In order to express the density of bacilli on a logarithmic basis, they recommend that the bacilli present in sections of 5 μ thickness be assessed on a 6 + scale as is done in the IB (section) or the BI (smear) indices. With a × 100 objective, 6+ signifies 1,000 bacilli or more per field, 5+ equals 100 or more bacilli per field, and so on, to 1+ equalling 1 or more bacilli per 100 fields. Half units are introduced when the count is in the upper range of a '+ number', which on a logarithmic scale is 0.7. The fraction of the dermis occupied by the granuloma is estimated with a low power (× 4 objective), to within 1/10; e.g., the granuloma may occupy 3/10 or 4/10, and the logarithm, to the base 10, of this fraction is added to the bacterial density figure to give the logarithmic index of biopsies (LIB). The logarithms required for the area of the granuloma have negative values, since they refer to fractions of 1; thus log. 0.6 is conventionally expressed as 1.8 which is in fact —0.2. For simplicity the logarithms are expressed as log. 1.0 = 0, log. 0.9 = —0.05, log. 0.8 = —0.1, log. 0.7 = —0.15, log. 0.6 = —0.2, log. 0.5 = —0.3, log. 0.4 = —0.4, log. 0.3 = —0.5, log. 0.2 = —0.7 and log. 0.1 = —1.

Whereas IB and BI can be no more than indices, the LIB forms a basis for crude counts and, if the size of the fields is known, the number of bacilli per cmm. can be calculated. With a field size of 0.17 mm., if the granuloma is assumed to be evenly distributed, it can be calculated that with an LIB 1.0 there are 80-250 bacilli/cmm. of dermis and with an LIB 6.0 there are 8,000,000 or more/cmm.; thus the bacillary content represented by these indices would usually be of the order 10^5 and 10^{10} per ml. respectively.

By a similar procedure the index could be modified to express a number of viable (solid-staining) bacilli present. If the percentage of solid organisms was 20, the proportion would be 0.2, the log. of which is —0.7. If the LIB was 4.3, the LIB (viable) would be 4.3 minus 0.7 or 3.6.

2. In the second paper, the author assessed the use and limitations of the indices IB, BI and LIB by comparing the results of the values calculated from observations made on patients before treatment and during the course of sulphone therapy. He shows that the random errors of biopsy indices are relatively small and that the rate of fall of the LIB during treatment is about twice that of the smear BI. The independent assumption of alterations in bacterial density of size and granuloma, which is made possible by the LIB shows some significant differences on the mode of responses to treatment by lepromatous and borderline leprosy patients, and the value previously placed on the IB index for assessing response to treatment as an aid to defining the TT-LL groups is fully confirmed.

S. R. M. Bushby.

5. **Cutaneous sarcoidosis and tuberculoid leprosy. A comparative histopathologic and histochemical study,** by T. Ramasoota, W. C. Johnson and J. H. Graham. *Arch. Derm.*, 1967, **96**, 3, 259-68.

A comprehensive histological and histochemical study of cutaneous sarcoidosis and tuberculoid leprosy was made to evaulate their differential diagnosis. Biopsies were made from 47 patients with sarcoidosis and from 45 with leprosy, and the results are described in detail and illustrated.

It was confirmed that the 2 conditions can be distinguished if cellular invasion of nerve bundles or the presence of acid-fast bacilli can be demonstrated, either of which is pathognomonic of leprosy. Other features, though not diagnostic one way or the other, were useful indicators. Invasion of the arrector pilorum muscles was frequent in leprosy and probably resulted from infiltration of the nerve supply. Fibrinoid degeneration, found at the centre of the tubercle in 58% of sarcoid specimens, was not present in leprosy. Elongated or cord-shaped tubercles are said to be characteristic of tuberculoid leprosy. A number of other features showed quantitative differences between the two conditions hich were of limited diagnostic value.

(In such a thorough study silver impregnation of nerves should have been included; but it is nevertheless a useful account of the histological differentiation of the two diseases.)

D. S. Ridley.

6 **The 'Lucio phenomenon' in diffuse leprosy,** by R. S. Donner and J. A. Shively. *Ann. Intern. Med.*, 1967, **67**, 4, 831-6.

The authors describe the case of a Mexican woman who had spent the previous 7 years in Texas and who developed a soft-tissue sarcoma of one leg. After amputation and a mild local infection she developed fever, severe anaemia, and skin lesions typical of those seen in Lucio's phenomenon (*Trop. Dis. Bull.*, 1949, **46**, 1053). It was then noticed that her eyebrows and eyelashes were absent, and her skin was diffusely thickened; skin smears showed large numbers of acid-fast bacilli. The authors emphasise the difficulty of diagnosing diffuse lepromatous leprosy and also the similarity of Lucio's phenomenon to the form of haemorrhagic cutaneous anaphylaxis due to autosensitisation to deoxyribonucleic acid. The reacting lesions are well shown in a photograph of the patient's face.

W. H. Jopling.

7. **Clinical evaluation studies in lepromatous leprosy. Sixth series: Effect (on lepra reaction) of supplementing DDS with dexamethasone, methandrostenolone, or mefenamic acid,** by J. A. Doull *et al. Int. J. Lepr.*, 1967, **35**, 2, Pt. 1, 128-39.

This study is a continuation of the carefully planned and carefully controlled drug trials that have been made in two Philippine leprosaria, Cebu and Central Luzon. The object was to determine the value, if any,

of 3 drugs in the prevention and treatment of lepra reaction when added to standard dapsone treatment. These drugs were: dexamethasone; mefenamic acid, a non-steroid drug with an anti-inflammatory action 5 times that of acetylsalicylic acid; and methandrostenolone, an anabolic steroid possessing little if any anti-inflammatory or cortisone-like property. The well-known standards of case admission, clinical and bacteriological assessment, and accurate recording we have come to expect of the trials were followed.

The double-blind trial began with 400 patients suffering from lepromatous leprosy, most of whom had received no previous treatment; of these, 346 remained for statistical analysis at the end of the 24 weeks' trial. The patients in the matched groups all received dapsone in a daily dose of approximately 2.5 mgm. per kgm. body weight (or 15 mgm. per kgm. per week), this maximum being reached after 8 weeks of treatment.

The trial drugs were given in daily doses (except Sundays) of 1.5 mgm. (dexamethasone), or 10 mgm. (methandrostenolone), or 750 mgm. (mefenamic acid). Between 80 and 94% of the prescribed doses were actually taken.

At the end of the trial period, 35% of the patients were considered to have improved, with an overall reduction of 14.5% in the bacteriological index (as calculated from 6 skin sites, and 2 from the nasal mucosa). No prophylactic or curative value could be attributed to any of the drugs used at the stated doses to supplement standard dapsone therapy; in fact, patients taking dexamethasone had more severe attacks of erythema nodosum leprosum (ENL) than those on dapsone alone. The latter had fewer and shorter attacks of ENL than those taking a supplementary drug.

Recurrences of ENL were noted in more than 90% of patients who had ENL at the beginning of the trial, but in only 52% of those in whom ENL was initially absent. Patients who seemed likely to undergo ENL were those suffering from more advanced lepromatous disease, with slighter tendency to borderline features, and they tended to have had longer sulphone therapy previously. It seemed that some patients were inherently more prone to develop ENL than others.

Patients who received methandrostenolone experienced a moderate increase in body weight.

No instance of drug intolerance occurred or side-effects attributable either to dapsone or to one of the supplementary drugs employed, except for one patient ad transient moon-face.

S. G. Browne.

8. **Inhibition of haemaggregation by lepromin and other mycobacterial substances,** by C. S. Goodwin, D. A. Tyrrell, B. Head and R. J. W. Rees (Correspondence.) *Nature*, London, 1967, Dec. 9, **216**, 1019-20.

Human erythrocytes in glucose buffer solution at *p*H 5.0-5.8 autoagglutinate and this is prevented by the addition of a variety of agents including tuberculin. In this study the authors show that preparations of *Mycobacterium leprae*, *Myco. lepraemurium* and other mycobacteria inhibit haemaggregation.

The preparations were dialysed to remove sodium chloride and each was titrated by the double-dilution, chess-board technique against fresh Group A human red cells in the buffer at *p*H values ranging from 5.0 to 5.7; in some experiments the red cells were treated overnight with 0.1% trypsin and, although 4-fold differences in inhibition titre were observed between these treated and untreated cells, the mean results were similar.

The titres of inhibition observed were 1 : 1280 and 1 : 3200 with lepromin from whole *Myco. leprae* or with cytoplasmic fractions from them; 1 : 80 with *Myco. lepraemurium* from rats, either as washed bacilli or cell walls and 1 : 160 with cytoplasmic fractions from them; 1 : 80 with H37Ra as whole bacilli, 1 : 20 with cell walls but 1 : 1024 when their cytoplasmic fraction was used.

An extract of normal skin was itself strongly inhibitory to haemaggregation so it could not be used to help in deciding whether the activity of lepromin is due to a component of the bacilli or to a product of the skin but the authors consider that it is most likely due to the former.

S. R. M. Bushby.

The following 8 abstracts are reprinted, with permission, from *Trop. Dis. Bull.*, 1968, **65**, 6:

9. **Détermination de la viabilité des mycobactéries de la lèpre à l'aide du procédé cytochimique** (Staining method for viability of *Mycobacterium leprae*), by S. V. Biryukova. *Problemy Tuberk.*, 1967, **45**, 12, 64-7. (In Russian.)

A staining method for *Mycobacterium leprae* is described, which enables a differentiation to be made between viable and non-viable organisms.

Films from examined material are prepared in the usual way and fixed over a flame (short exposure to the heat does not affect the staining properties of viable bacteria). Then the film is stained with 1% malachite green warmed to 70°C. The stain is kept on the film for 5-10 minutes at room temperature. Afterwards it is washed in water and stained with fuchsin (aqueous solution) for 2-5 minutes. Next the stained film is decolorised with 8% nitric acid, washed in water and dried. Viable bacteria appear as green, non-viable as red, bacilli. The structural changes in DWA in non-viable bacteria are related to the loss of ability to retain the first stain.

The author carried out experiments on white mice infected with *Myco. leprae* and found by this method a significant increase of non-viable organisms in animals treated with antimycobacterial drugs (solusulphol (? solasulfone = solapsone) and ethionamide).

Owing to difficulties in the cultivation of *Myco. leprae* this staining method could be used in the evaluation of the effects of chemotherapy in leprosy.

W. Odrzywolski.

10. **Studies of immune mechanisms in leprosy. I. Depression of delayed allergic response to skin test antigens,** by W. E. Bullock *New Engl. J. Med.*, 1968, **278**, 6, 298-304.

It is not certain to what extent the anergy to lepromin

of patients with lepromatous leprosy is specific. Although the evidence regarding a possible anergy to other antigens is somewhat conflicting, there have been reports of diminished sensitivity to tuberculin and to *Candida albicans* extract in lepromatous leprosy, and also to a lesser degree in tuberculoid leprosy. In this paper the sensitivity to lepromin (Mitsuda and Dharmendra types), purified protein derivative (PPD) trichophytin and *C. albicans* extract at various strengths was tested in both forms of leprosy with reference to the length of treatment and other factors. The induction of contact type delayed hypersensitivity to picryl chloride was studied similarly. 107 patients and 30 control subjects were used in the tests.

The percentage of positive reactions to each antigen was lower in the patients with leprosy than in the control subjects, and the depression of sensitivity was observed in both tuberculoid and lepromatous types of infections, though it was greater in lepromatous leprosy. The only exception to this result was the 48-hour lepromin reaction in tuberculoid patients, who produced the normal percentage of positives. With all antigens the depression of sensitivity was greater in patients who had received less than 18 months' treatment than in those who had had over 18 months', especially among lepromatous patients; i.e., the incidence of positives tended to revert to normal after prolonged treatment. (The increased incidence of lepromin reactions after treatment might be explained by borderline reactions among the borderline lepromatous patients who were included in the lepromatous group.) But there were no distinctive differences among the patients who suffered from erythema nodosum leprosum, nor among those who underwent tuberculoid reactions.

These interesting results indicate that in leprosy there is a generalised depression of the delayed allergic inflammatory response.

D. S. Ridley.

11. **DDS prophylaxis against leprosy,** by R. V. Wardekar. *Lepr. India*, 1967, **39**, 4, 155-9.

This paper describes a trial in which the prophylactic value of dapsone (DDS) is compared with that of a placebo in 54 villages in the Bobbili region of Andhra Pradesh. The trial included all healthy persons aged less than 25, and the villages were divided into 27 test (dapsone) villages and 27 control (placebo) villages. The numbers of persons involved were roughly 11-12,000 in each group, and all those who developed leprosy during the period of the trial were transferred to treatment clinics. No survey was made during the first 9 months, but it was noted that during this time 84 persons in the dapsone group and 80 in the control group reported with leprosy lesions.

In the first survey, covering the 10th to 21st months of the trial, there were 2.53/1,000 cases of leprosy in the dapsone group (1 lepromatous and 28 non-lepromatous), and 4.79/1,000 in the control group (3 lepromatous and 51 non-lepromatous). In the second survey, covering the 23rd to 32nd months, there were 1.17/1,000 cases of leprosy in the dapsone group (1 lepromatous and 13 non-lepromatous), and 5.36/1,000 in the control group (4 lepromatous and 61 non-lepromatous)—a statistically significant result.

W. H. Jopling.

12. i. **A preliminary review of the experimental evaluation of drugs for the treatment of leprosy,** by R. J. W. Rees. *Trans. R. Soc. Trop. Med. Hyg.*, 1967, **61**, 4, 581-95.

ii. **The evaluation of drugs for leprosy: bacteriological considerations,** by D. S. Ridley. *Ibid.*, 596-600.

iii. **The clinical evaluation of drugs for leprosy,** by S. G. Browne. *Ibid.*, 601-7.

i. It was shown by Shepard (*Trop. Dis. Bull.*, 1961, **58**, 214) that human *Mycobacterium leprae* will multiply to a limited extent in the footpads of mice, until the number of about 10^6 is reached. Then multiplication ceases, presumably owing to immunological causes. Rees has found that if mice are thymectomised and irradiated, so as to suppress their immunological reactions, the bacilli can continue to multiply up to 10^9. This multiplication in the footpad can be used to test the activity of drugs against *Myco. leprae in vivo*. By this test dapsone, sulphadimethoxine, sulphormethoxine, diphenylthioureas (e.g., thiambutosine), thiacetazone, Riminophenazine (B663), streptomycin, isoniazid, *p*-aminosalicylic acid and capreomycin have been shown to be active, but ethambutol, ditophal, and pyrazinamide were inactive; cycloserine was weakly active. Human leprosy bacilli in the footpad of mice are extremely sensitive to dapsone, a daily dose of 0.02 mgm./kgm. being enough to prevent growth. This technique has also been used to prove that 8 strains of human bacilli, taken from 8 patients in Malaya who failed to respond to sulphone treatment, had definitely become resistant to dapsone. Such cases are, however, rare.

ii. Ridley describes tests for the response of patients to treatment based upon (i) the percentage of solid-staining bacilli (i.e., viable bacilli) in lepromatous lesions (the Morphological Index) and (ii) the bacilli in smears, expressed in a logarithmic scale (the Bacteriological Index). The former is more important for short term trials, the latter for long term trials.

iii. Browne describes the numerous difficulties of clinical trials, owing to the protean nature of leprosy, the variability of patients and many other causes. He considers that there is need for: (*a*) a long-acting chemical prophylactic; (*b*) a rapidly-acting mycobactericidal drug; (*c*) an agent to accelerate the removal of mycobacterial debris from the tissue; and (*d*) a drug to minimise tissue sensitisation and sensitivity reactions.

(This valuable symposium should be studied in the original by all interested in leprosy.)

F. Hawking.

Transmisión de la lepra humana a la alantoides del embrión de pollo (Transmission of human leprosy in the chick embryo), by J. G. Prieto. *Anais Inst. Med. Trop.*, 1965, **22**, 1/4, 179-83, 12 figs. on 11 pls.

The English summary appended to the paper is as follows:—

'We achieved the appearance of macroscopically visible nodular lesions in allantois of chicken inculated with different types of human leprosy. Histologically, these lesions were constituted by a leprotic granuloma with vacuolated cells inside which were found amorphous masses and acid-resistant particles.

'Via the electronic microscope we demonstrated the existence of some bacilli and observed the structure of the amorphous masses and acid-resistant particles that suggest a cyclic development of *M. leprae*, which, in some circumstances, may originate large L forms, spheroblasts and probably filtrable particles.'

6. **Las formas sub-microscópicas del** *M. leprae* (Sub-microscopic forms of *Mycobacterium leprae*), by J. G. Prieto, G. Gonzalez and M. L. Alonso Puertas. *Medna Cutánea*, 1967, **2**, 1, 51-68.

The English summary appended to the paper is as follows:—

'Description of the transmission of different types of human leprosy, lepromatous, tuberculoid and indeterminate, into the chorio-allantoic membrane of chicken embryos.

'Inoculation of this material provokes yellowish nodules umbilicated in the centre, in the allantoids of the chicken. These may be transmitted in serial form, in one case up to the 14th passage. Histologically these nodules are initially composed of a dense accumulation of vacuolated, histiocytic cells, similar to those of human leprosy. After the 6th or 7th passage, this structure changes into an accumulation of histiocytic leprosy of Wade.

'Only by inoculating bacillary material can one observe any acid-fast bacilli in the first passage and after the 3rd or 4th passage, only acid-fast granules and some partially acid-fast material in spherical forms that are larger and irregular. Strangely enough, with the electron-microscope the following 3 types of formations can be observed:

'Ovoid bodies, wrapped in membranes, similar to those described by Imaeda in experimental hamster leprosy and which are, perhaps, as this author maintains, degenerated bacilli; formations wrapped in a clearly visible membrane, containing very dark spherical or ovoid forms which could conceivably be large L forms; rounded particles, dark-centred and surrounded by a light marginal zone, virus-like and possibly small L forms.

'In bacteriologically positive human leprosy one observes, above all, changes in the mitochondria which lose their cristae and myelin formations, particularly intense in lepromatous leprosy.

'Description, with numerous electron photomicrographs, of the ultrastructure of *M. leprae* and of the globi, as well as some epidermal features not hitherto described.

'Some of the electron photomicrographs show a particularly noticeable presence of the same formations to be found in experimental leprosy of the allantoid.

'In biopsies of incipient tuberculoid or indeterminate lesions in which no acid-fast bacilli appear but only acid-fast dust, the ultra-structure of these forms is described. Membrane-wrapped forms are to be found, containing tiny, very dark spherical bodies. At numerous points of the cytoplasm, these forms are loose-floating and almost identical to the virus-like particules observed in profusion in experimental leprosy of the allantoid.

'The above findings are fully discussed and the hypothesis advanced is that in addition to the typical acid-fast bacillary forms of *M. leprae*, infra-microscopic filterable forms also exist, thus explaining the enormous percentage of leprous lesions devoid of bacilli.

'The allantoid of the chicken embryo would prove to be an exceptionally appropriate form of culture for the development of these forms. The brief time lapse, maximum 5 days, in which observation of the evolution of these lesions can be made, does not allow observation of the transformation of this phase of the cycle of evolution of *M. leprae* in acid-fast and bacillary forms. In order to achieve this, it would become necessary to be able to inoculate this material into longer-living biological systems.

'Possibly this observation coincides with the findings of Shepard who, after inoculating *M. leprae* into the footpads of rats, observed some months later the temporary disappearance of the acid-fast bacillary forms which later reappeared again.'

The following 6 abstracts are reprinted, with permission, from *Trop. Dis. Bull.*, 1968, **65**, 7:

17. **Lepromin and tuberculin reactivity in adults not exposed to leprosy,** by C. C. Shepard and E. W. Saitz. *J. Immunol.*, 1967, **99**, 4, 637-42.

A group of 73 inmates of a penitentiary, all males and all 'whites', aged 25-45 years, was skin-tested with Mitsuda-Hayashi type lepromin (biologically standardised, and containing 2.5×10^7 acid-fast bacilli per ml.), and also with tuberculin and mumps antigen.

Although none of the men had been exposed to leprosy, all showed positive reactions to lepromin, of various degrees of intensity from 4 mm. upwards. There was some correlation between the Fernandez and the Mitsuda reactions, but none between the tuberculin and the lepromin reactions apart from a tendency for the degree of positivity of the lepromin reaction to increase with the size of the tuberculin reaction.

The assumption that the lepromin reaction is determined by prior exposure to leprosy bacilli or by sensitivity to tuberculin is not supported by these findings, and the origin of the lepromin sensitivity in group is left unexplained.

S. G. Browne.

The isopathic phenomenon in infiltrated tuberculoid and macular tuberculoid leprosy. A comparative histologic study of the tissue response produced by cotton pellet implantation and lepromin injection, by A. H. Klokke, A. Bhaktaviziam and B. Subramaniam *Int. J. Lepr.*, 1967, **35**, 4, Pt. 1, 477-87.

'Forty-five patients with tuberculoid leprosy were examined. These were distributed in 4 groups: I,

infiltrated tuberculoid, 12; II, macular tuberculoid with a single macule, 9; III, maculoanesthetic, 10; and IV, low-resistant tuberculoid, 14. In 38 patients bacteriolcgic and histologic examination was carried out of skin lesions and reactive granulomas produced by cotton pellet implantation and lepromin injection. In 7 patients (included in group I) a suspension of normal tissue was injected.

'This study demonstrated the existence of an isopathic phenomenon in tuberculoid leprosy. In the majority of patients a tuberculoid tissue response was obtained. Both cotton pellets and normal tissue provoked granulomas reflecting the same pattern of immunologic response, which was of lower grade compared to that produced by lepromin. The outcome supports the hypothesis that the Mitsuda reaction produced by lepromin is a kind of foreign body reaction.

'A sliding scale of decreasing tuberculoid response was seen in patients ranging from group I, the highest mean grade, to group IV, the lowest mean grade. Macular tuberculoid leprosy (groups II-IV) proved to be a distinct variety of leprosy of tuberculoid immunologic status.

'Ths histology of lepromin-provoked granulomas in patients with disseminated macules (groups III and IV) gave evidence more clearly of the host's exact tissue response than mere histologic examination of skin lesions.'

19. **A study of the conduction velocity of sensory fibres of the ulnar nerve in leprosy,** by M. S. Dash. *Int. J. Lepr.*, 1967, **35**, No. 4, Pt. 1, 460-69.

'The conduction velocity of the sensory fibres of the ulnar nerve has been studied in leprosy patients.

'Sensory potentials have been recorded from the afferent nerves supplying anesthetic areas, and therefore a loss of sensation in leprosy does not necessarily mean destruction of all nerve fibres. This conforms with the histologic observations of Weddell, Jamison and Palmer and of many other workers, who noted the presence of healthy nerve fibres in leprosy lesions.

'It has been shown that a significant reduction of the conduction velocity occurs in all forms of leprosy. The cutaneous afferent fibres are affected more than the muscle afferents.

'A prolongation of the refractory period of the nerve fibres probably precedes the reduction of velocity. The significance of this finding is discussed.

'It appears that the cutaneous receptors are deranged, but not totally destroyed, over all anesthetic areas in leprosy, and sensations can be induced to reappear.'

20. **Observações preliminares com sulfamida de eliminação ultra lenta no tratamento da lepra** (Preliminary studies on a long-acting sulphonamide in the treatment of leprosy), by A. C. Pereira, Jr.. *Anais Bras. Derm.*, 1967, **42**, 1, 35-45.

The English summary appended to the paper is as follows:—

'The author reports the treatment on 23 leprosy patients with Ro 4-4393 sulpha for about one year. Nine cases of lepromatous, 2 of borderline and 12 of tuberculoid leprosy.

'Satisfactory results were obtained, comparable to the results obtained with DDS.

'The author also shows the remarkable tolerance of the patients to this drug and its simple administration, and in view of its ultra-slow elimination it can be used in weekly doses.

'The author, nevertheless, remarks the brief period of time of this observation in order to draw definite

Talidomida nas reações lepróticas (Thalidomide in lepra reaction) by L. S. Netto. *Revta Bras. Med.*, 1967, **24**, 9, 760-63.

The author laments the severity of the leprotic reactions he has seen in patients under sulphone treatment which often necessitate its suspension. In an effort to find drugs which will suppress this, he has tried, among others, steroids and antimonials which have proved the best so far, but in view of the report of favourable results after the use of thalidomide he tested this drug on 10 patients aged from 20 to 50 years. The dosage varied, but in most of the patients it was 100 mgm. daily. This enabled the sulphone treatment to be resumed and he states that the improvement seen in the leprotic reactions was quite remarkable. He considers that the optimum dose of thalidomide is 100 mgm. daily and that this drug should now be included in the list of first line drugs in leprosy. However he advises caution in its use in female patients.

(See also *Top. Dis. Bull.*, 1966, **63**, 285, 1200, 1344; 1967, **64**, 380.)

W. K. Dunscombe.

22. **Prophylactic value of DDS against leprosy—a further report,** by Dharmendra, S. K. Noordeen and K. Ramanujam. *Lepr. India*, 1967, **39**, 3, 100-106.

'An interim report on the investigations regarding the prophylactic value of DDS amongst intra-familial child contacts of infectious patients of leprosy had been published earlier, covering a period of 30 months of the study proper, up to the end of October, 1965. Full particulars about the investigations and the detailed methods of work were included in that report. (*Trop. Dis. Bull.*, 1967, **64**, 1332.)

'The investigations have been continued and the present report includes findings made up to October, 1966, i.e., over a period of $3\frac{1}{2}$ years of the actual observations.

'During the entire period of $3\frac{1}{2}$ years, 60 leprosy patients, 57 of the non-lepromatous and 3 of the indeterminate type, have been detected in the 632 contacts studied up to October, 1966. Of these 60 patients, 41 (including the 3 indeterminates) arose amongst the 316 contacts in the 'Control' group, and 19 amongst the same number of contacts in 'Prophylaxis' group. This gives an incidence of 13% in the control group, and 6% in the prophylaxis group. The difference in the incidence of the disease in the 2 groups (6% against 13%) is statistically highly significant ($t=3.0$, $p<0.01$).

'The difference seen in the incidence of the disease in the 2 groups has been due entirely to the difference seen in this respect in the contacts up to 10 years of age. No difference was observed in the contacts of the age-group 11-15; however, the number of contacts in this age-group was too small (about 50 in each group) to permit any definite conclusion.

'The effect of the prophylactic treatment was not evident till 9 months after starting the treatment. It then became evident, and has been maintained throughout the period of observation. Of the 13 cases amongst the contacts up to 10 years of age, all but 4 occurred in the first year of observation; on the other hand, amongst contacts of the same age-group in the control group, the 33 patients were distributed throughout the period of observation.

'Thus, the further results obtained since the last interim report have confirmed the earlier finding regarding (i) the protective value of DDS against leprosy, and (ii) the need for starting the prophylactic treatment at a very early age in case of intra-familial contacts.

'The study was not designed to specially find out if the prophylactic DDS had any toxic effects on the treated children. However, during the frequent follow up of the contacts, no obvious signs of the toxicity were observed, in particular it may be stated that no drug dermatitis was observed.

'In 137 of the 316 contacts in the prophylaxis group, DDS treatment has been stopped as they have completed 3 years of prophylactic treatment, and their "source" have all along been bacteriologically negative. They will now be followed up and periodically examined to see the long-range effect of the prophylactic treatment.'

Reports

Ghana Leprosy Service

Report covering the years 1963-1967

This Report spans a period during which increasing emphasis was placed on domiciliary treatment of leprosy patients, on increasing integration of the leprosy service with the developing static and mobile rural health service, and on the importance of diagonosis of new cases and rehabilitation of the old.

A total of 21,441 patients are now under treatment, which represents a decrease of about 4,000 compared with the total in 1963. The lepromatous rate is 12%. About 4% of the patients are treated in leprosy settlements, the majority of the remainder receiving treatment from mobile clinics.

Hitherto, case-finding survey teams have confined their attention to leprosy, but in future the diagnosis of other endemic diseases (such as tuberculosis) may be added to their duties, just as it may be desirable on general and financial grounds for tuberculosis to be treated in domiciliary fashion together with leprosy.

The leprosaria are in process of becoming hospitals for leprosy sufferers needing in-patient treatment for acute complications—a commendable trend.

Oral dapsone continues to be the mainstay of treatment, the dose generally given being of the order of 4-500 mgm. weekly. Parenteral dapsone is given on occasion. Ditophal and long-acting sulphonamides have been used also.

Occupational therapy (mainly agriculture) and village craft training are now available for a small proportion of patients. But most of the patients, being treated in their own homes, do not suffer social dislocation or require expensive and perhaps artificial rehabilitation to prepare them for re-entering the village community they have never left.

An interesting feature of the mobile treatment scheme is that the weekly treatment runs have recently been converted into monthly runs, in order to conserve motor transport. It will be instructive to note patient reaction to this innovation and its effect on regularity and efficacy of treatment.

The tendency to enlist the co-operation of health centres and their staffs in leprosy treatment and control is all to the good, and should be encouraged in other countries wherever possible.

An attempt at reconstructive surgery on simple lines has added to the effectiveness of the control scheme.

Whole population survey teams find about 7 people suffering from leprosy out of every 1,000 examined. This figure is in approximate keeping with the estimated total number of leprosy sufferers for the whole of Ghana, viz., 50-60,000. Only when a higher proportion of patients is under regular treatment can the medical and administrative authorities allow themselves to rest on their laurels or to relax their vigilance and their efforts.

S. G. Browne.

St. Luke's Hospital, Peikulam, India

The Annual Report for 1967 of the work of St. Luke's Hospital makes interesting reading, and illustrates once again what one devoted doctor (aged 75) can do to meet the leprosy needs of a rural area. It also shows the value of co-operation between such organisations as the British and German Leprosy Relief Associations, and local church groups and individuals. New wards have been built for in-patients, and a sufficient supply of water ensured both for the hospital and for the erstwhile barren land destined for the agricultural training section of the rehabilitation scheme. The work of education of the remote villager in the early signs of leprosy has disclosed an increasing number of self-diagnosed patients with small early anaesthetic skin lesions, who are given treatment at the out-patient clinic. Protective footwear, craft instruction, raising of laboratory standards, training of paramedical workers—are all accorded their rightful place in this expanding leprosy control scheme.

S. G. Browne

(1968)

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