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Editorial

COMMUNICATING

The word "communicating", together with its cognates, is fashionable in scientific literature today as well as in polite and earnest conversation. Such words may be bright and attractive when newly minted, but forfeit both their shine and their value with constant use. In the world of science, and particularly in the realm of leprosy, "communicating" indicates something real and genuine, something praiseworthy and, in fact, essential. Unless we do it and encourage it, we shall fail to take advantage of the new wealth of knowledge and the new investigative techniques that are now being made available.

And it is all too easy to rest on one's oars, to become smugly satisfied with old ways and familiar scenes, to develop an imperviousness to new ideas and novel methods. Clinicians and administrators, physicians and surgeons, field workers and (surprisingly) laboratory researchers may all be guilty of an unwillingness to communicate and to be communicated with.

Leprosy Review will provide an ever-open, two-way (or multi-way) channel for communicating. As in the past, it will be a public forum where those who have something to say will always find those on the look-out for something worth listening to. Given the desire to understand, and the will to make the effort to learn the vocabulary and to become acquainted with the essential language of the newer specialities, there should be no real or lasting difficulty in making oneself understood or in understanding what the other man is trying to tell us.

Unlike the dilettante Athenian loungers who only wanted their fancy tickled by some "new thing", our readers will critically welcome fresh reviews of old assumptions and re-examinations of some remaining *ex cathedra* dicta that have been passed down for generations. This will not mean the futile repetition of good work already done, or any wordy self-education in public, but it may well comprise some wholesome protest against the danger of being mesmerized by a name or an institution.

Leprosy Review will cast its net wide. It has already done so in the past few years. To adapt the old tag, nothing of interest to the leprosy worker will be alien to us. The research scientist in his laboratory will be wanting to share with medical workers in the field and in the clinic the results of his investigations. The time-lag between the laboratory and the field must be shortened, with due regard of course to severe scrutiny and critical appraisal. The worker in a distant leprosy clinic, cut off in some ways from the thrill of high-powered research, will on his part also have something worthwhile to communicate. If some of the outstanding problems of leprosy are going to be solved in the laboratory, with the co-operation of the helpful mouse and dedicated men, other problems-of transmission, vulnerability and refractoriness, and spontaneous regression-may well find their solution in the field.

Leprosy Review will encourage field workers to analyse their methods of leprosy control and to evaluate the results achieved, so that more effective measures may be developed for a most intractable public health problem.

Channels of communication are kept open by constant use. Whatever our specialized interests or immediate concerns, the ultimate, if unexpressed, aim of most of us is the control of leprosy, and we bend our diverse expertise and energies to this end. *Leprosy Review* will keep this end clearly in view, and publish "communications" that will stimulate and help all those whose concern is leprosy and leprosy control.

Of recent years, leprosy has emerged from the dark ages of superstition and has become scientifically respectable. The increasing seriousness of these new studies in leprosy, and their sheer scientific fascination, will, we hope, be reflected in the pages of *Leprosy Review*. All those working in leprosy—clinicians, laboratory workers, reconstructive surgeons—will find articles of interest and importance in its pages, while nurses and physiotherapists, prosthetists and medical auxiliaries (paramedical workers) will discover much that 's instructive and helpful. Non-specialist practitioners, who from understandable lack of time or interest glance merely at titles and summaries, will be kept abreast of new work in leprosy, both by original articles

ELEP Medical Commission

The Medical Commission of ELEP (Association of European Leprosy Organizations), composed of Drs. L. P. Aujoulat, S. G. Browne, Fr. Hemerijckx and Fr. Wegener, met in Brussels on 5 November, 1968, to discuss the medical aspects of diverse projects in which memberorganizations are interested. Thanks to the numerous official and unofficial contacts that the members enjoy in their own countries and abroad, it is possible to make the influence of the voluntary agencies felt in leprosy control schemes in many lands. Contact is maintained with W.H.O. and has been initiated with O.C.E.A.C., the Commission concerned with endemic diseases in the French-speaking countries of Africa.

An interim report on an epidemiological survey of leprosy in Morocco was received, and up-to-date news of the Adzopé Project (in the Ivory Coast) was given by Dr. Aujoulat.

Prospects for the creation of a Professorial chair of Leprology at the University of Dakar (Senegal) were welcomed, especially as it is hoped that the title-holder would be able to and abstracts of papers published elsewhere, and by authoritative reviews and symposia.

We hope that our correspondence columns will reflect both the critical acumen (and courtesy) of our readers and the great range and variety of experience in leprosy that they represent. Brief and pointed comments will always be considered for publication.

spend part of every year lecturing to Frenchspeaking medical students at the different medical schools in West and Central Africa, and include visits to the A.L.E.R.T. Project in Addis Ababa.

The ELEP-sponsored Leprosy Control Project at Dharmapuri (India) is now well under way. Dr. I. A. Susman has appointed paramedical staff and begun preliminary surveys of the area involved.

The Medical Commission of ELEP is concerned that medical priorities should be respected as far as possible in schemes sponsored either jointly or separately by the memberorganizations, while admitting that in some circumstances social and non-medical considerations may be equally important. The channelling into effective leprosy control work of moneys raised by voluntary organizations appealing to the general public often raises delicate questions where the emotional factor may conflict with long-term anti-leprosy strategy.

S. G. BROWNE

G 30 320 or B 663—Lampren (Geigy)

Of the many drugs investigated for their activity in leprosy of recent years, one of the most promising is B 663. This drug is one of a long series of rimino-phenaziné derivatives synthesized in the laboratories of the Irish Medical Research Council in Dublin. Its use in leprosy has been the subject of numerous publications, the first of which appeared in the pages of *Leprosy Review* some 7 years ago.

A slightly edited verbatim report of a Symposium on B 663, which was organized to precede the recent International Leprosy Congress, appears on pages 21 to 48 in this issue.

Trial of BCG Vaccination Against Leprosy in Uganda

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This further report from Uganda of the results of a trial of BCG vaccination against leprosy which was begun in 1960 and now has included more than 19,000 children, shows that among over 9000 unvaccinated children there were 174 cases of leprosy, whereas among a similar number given BCG vaccination there were only 27 cases. Thus, in these 2 comparable groups the attack rates per 1000 were 19.3 and 3.0 respectively, representing a reduction rate of 84%. It is pointed out, however, that once a leprosy lesion has begun to develop, BCG vaccination has no preventive value.

The Uganda trial of BCG vaccination against leprosy began in September 1960. However, its development and pattern had their roots in a series of leprosy surveys made in Uganda between 1952 and 1959 (Kinnear Brown, 1955, 1957, 1959). These surveys led to the establishment of a communally-built village system for the treatment of leprosy linked with field clinics, most of these being supervised from an established leprosy settlement. The Medical Research Council in Great Britain had for some years been considering the possibility of a trial of BCG against leprosy, and the Uganda Ministry of Health had encouraged certain epidemiological and immunological investigations which were of value in setting up the trial in that country.

Uganda lies on the equator at a mean altitude of 1230 m (4000 ft) and has an area of 238,000 sq. km (93,000 sq. miles). Its population of 6,000,000 is dispersed in family units. It is important to understand that this dispersed family unit is the basis of society and that there are no natural towns or villages. In Uganda, therefore, leprosy could be studied in an environment uncomplicated by the conditions which exist in countries with densely populated urban areas.

The surveys of leprosy in Uganda had suggested that a hot humid climate, overcrowding, and prolonged intimate contact, which are traditionally associated with leprosy, did not explain the variations in prevalence of the disease in the country. In Uganda, and in similar surveys in north-west Kenya, the prevalence varied widely, from 0 to 43/1000of the population. The higher rates were found in comparatively small groups that for geographical or ethnological reasons were isolated and had only limited external relationships. The lower rates were found among the larger sections of the population which were mobile and did not marry within a restricted circle. This was not a difference between tribes. because high and low rates occurred within the same ethnic group, depending on its mobility or insularity. These considerations emphasized the importance of constitutional factors and of relationship in the spread of leprosy (Kinnear Brown, 1959), and made understandable the low conjugal rate of infection and the comparatively low prevalence among people living in close contact in an unrestricted community. It was therefore decided to concentrate for the trial on children related to or in contact with known patients.

The area chosen was the Teso District, which has an area of 11,500 sq. km (4500 sq. miles) and a population, dispersed as described, of some 450,000. The prevalence of leprosy in the 1950's was 25/1000 population of all ages. Among children under 15 the prevalence was 9/1000. Of the patients, about 6 to 8% had the lepromatous type of the disease. Although the population is widely dispersed, it is grouped in 180 administrative units, called eitelas, of which 140 were included in the trial.

ADMISSION OF CHILDREN INTO THE TRIAL

The eitelas were visited in turn and the children related to, or in contact with, known patients were produced by the chiefs, health staff, and leprosy assistants, given a serial number, carefully examined to exclude leprosy, photographed with an adult relative to facilitate later identification, and given a Heaf tuberculin test. The presence of an adult in the photograph was often of crucial value in identifying the child. The child's serial number was included in the photograph.

An identity card with a duplicate phocograph was given to each child when the tuberculin test was read a week later, but there was no indication on the card or the photograph as to whether the child had been vaccinated or not. The tests were read in the order in which the children came, which was not in the order of their serial numbers. Alternate children who had weak positive or negative reactions (Grade II or less) were vaccinated immediately after the test had been read. Of those with strong positive reactions (Grade III or IV), none were vaccinated, but all were followed up in the trial.

The intake lasted from September 1960 to. September 1962, by which time 17,397 children had been admitted to the trial, comprising 8152 unvaccinated, 8149 vaccinated, and 1096 with strong positive tuberculin reactions. When subdivided into 2-year age groups the numbers of the vaccinated and unvaccinated in each age group were so close as to be almost identical. We thus had 2 groups between which the only difference was the factor of BCG vaccination.

FIRST FOLLOW-UP EXAMINATION

The first series of follow-up examinations began in May 1963, and ended in May 1964; 227 of the trial children had died, mostly in the youngest groups, and 718 were not seen. Thus 94% of those admitted to the trial were re-examined after an average interval of $2\frac{1}{2}$ years. At the same time, 1926 children newly born into the trial families were admitted, alternate children being vaccinated. This represented a valuable addi

and brought the total up to more than 19,000.

SECOND FOLLOW-UP EXAMINATION

The second series of follow-up examinations began in July 1964 and continued until March 1966. In all, 91% of the children were examined after an average interval since intake of $3\frac{1}{2}$ years; 103 children had died and 1621 were not examined, but 367 of those not seen during the first follow-up were recovered. Moreover others, who were not seen at the first or second follow-up examination, have been recovered in the course of the third follow-up, which is now reaching its termination. This third follow-up began in July 1966 and should be completed early in 1969.

PROCEDURE AT FOLLOW-UP EXAMINATIONS

Each local health inspector has a register of the trial children in his area, with full particulars except for their tuberculin or vaccination status. Lists are also prepared of children who have transferred permanently, or temporarily, into a particular area. These are used by the chief and health inspector to summon the children to a convenient centre for examination.

At each follow-up examination the procedure is the same. Children are identified from their cards and photographs as they come, or their names are called out from the health inspector's register. The sub-chiefs, clan leaders, and heads of families assist as necessary in identification and in producing missing children. The filed field record is stamped on the back with the date. Adhesive paper is then placed over the site where any scar exists or would have existed had BCG vaccination been carried out.

When about 20 children have been collected, they are taken for primary screening by experienced leprosy assistants who have worked with us (J.A.K.B. and M.M.S.) for 15 years; periodically one of us in the field supervises the screening. All examinations are made in open sunlight, with the children undressed but given adequate privacy. Children showing any lesion in the skin, or alteration in colour or texture, are referred to us. In addition, the person who checks the field record fastens a black cord on the wrist of any known leprosy patient without indicating when any lesion was first noted, or where the lesion was situated. Similarly, a white cord is fastened round the wrist of anyone who has had a suspicious lesion, without further details. When a decision is reached by us about a referred lesion, the description is dictated and entered on the field record. The diagnoses are thus made without knowledge of the group to which a child belongs. The adhesive paper concealing any vaccination scar is kept in position by the children throughout the session.

DIAGNOSIS

In such a vast area the diagnosis in the field has to be clinical, and the evolution of the lesion or lesions is an important aspect of it. The cases of leprosy recognized were those in whom the history was that of a chronic hypopigmented lesion or lesions, flat or with elevated centres or margins (according to type), often with pilot patches. Such lesions could have healing centres and active coppery margins. There was often evidence of nerve involvement, such as tactile or thermal anaesthesia. The nerve trunks were always examined carefully for enlargement and tenderness. The relationship of a child to a known patient such as the mother or father was never a factor in diagnosis. So far, no cases suggestive of lepromatous leprosy have been recognized in the trial children.

RESULTS

Prior to the main intake we visited a few areas under trial conditions in order to gain the experience on which much of our field detail has been built. The children in these areas are still followed-up to maintain interest, but they have been excluded from the results now presented. There were also a number of children who failed to attend for the reading of the tuberculin test; they too have been followed-up for the same reason, but have been similarly excluded from the results. A total of 395 children had leprosy at the time of the first examination and have been followed-up in their own interest, and in ours, to trace the evolution of the disease; they naturally do not contribute to the assessment of vaccination (Table 1).

TABLE 1 BCG and leprosy in Uganda up to June, 1968

Group	Total no. of	1	Per- centage		
1	children	No.	Rate/1000	red uction	
Unvaccinated	9036	174	19.3		
BCG vaccinated	9052	27	3.0	84	

The number of children who had developed leprosy up to the middle of June 1968 was 214. Of these 174 were controls, and 27 had been vaccinated. This represents a protection rate of 84% attributable to the BCG vaccination. The other 13 children with leprosy had strong positive tuberculin reactions at intake. Analyses by age show that this protection does not depend on age (Kinnear Brown *et al.*, 1966, 1968).

It was expected from previous experience that a proportion of these early leprosy lesions in children would resolve spontaneously. It was, therefore, the general policy to observe lesions without giving treatment, to study their natural course, and to treat only those with particularly extensive or progressive lesions. Treatment was recommended by us in a small proportion of cases, but every parent was also free to apply for treatment for a child at any time, and some of them did so. At the end of the first follow-up 17% of the patients seen at the preliminary examination had been admitted to treatment, in 28% the lesions were extending, and in 29% they were resolving or had resolved without treatment; in the other patients the lesions were static.

At the end of the second follow-up the progress of the patients detected during the first follow-up was observed; 23% had been admitted to treatment, in 40% the lesions were extending, and in 25% they were resolving or had resolved without treatment. There has thus been no attempt to delay treatment to the detriment of the child, nor has the natural course of the disease been obscured by precipitate treatment of hypochromic lesions. It has been valuable to be in a position to observe how early leprosy lesions can recede or progress in the absence of treatment, something which is not possible in treatment institutions. These findings have confirmed that the historical evolution of the lesions is an important and often decisive factor in establishing the diagnosis and the need for treatment.

As a result of this study we can divide the patients into at least 5 groups:

- (1) Those whose lesions extend steadily but at varying speeds.
- (2) Those whose lesions appear to resolve, in some cases quickly and in some slowly.
- (3) Those whose lesions *extend* after a long period of no apparent change.
- (4) Those whose lesions *resolve* after a long period of no apparent change.
- (5) Those whose lesions return, sometimes violently, after apparent complete resolution.

Lesions other than leprosy were noted throughout the trial. The differentiation of some was difficult, especially if local applications had been used. A definite decision only became possible when the child was seen on subsequent occasions and a historical assessment could be made. In the first year 154 children with such lesions were admitted to the trial, but the findings among them have been kept separate. Of these 154, 29 were subsequently confirmed as having leprosy; 5 had been tuberculin-positive, 12 unvaccinated and 12 vaccinated. The inference is that once a leprosy lesion has begun to develop, however vague it may appear, BCG vaccination has no preventive value.

CONCLUSION

In the early leprosy found among children in Uganda, BCG has provided more than 80% protection for a period of 6 to 7 years. However, BCG has not given any protection against leprosy in the small group with ill-defined lesions. There was no difference in the response to treatment whether the child developing the disease had been vaccinated or not. The personal experience of one of us (J.A.K.B.) both in West and in East Africa, has shown how much the pattern of leprosy has changed during the last 40 years. This must be partly due to the introduction of drugs specific against leprosy, and also to drugs specific against the other serious diseases which used to dominate the scene. The effect of BCG vaccination has been studied in young children, among whom the type of leprosy now seen is usually early and uncomplicated by other conditions. It is not possible to assess what the results might have been in the past, with so little armament against leprosy, and so many concomitant diseases.

These results are very encouraging. Nevertheless, it is clearly necessary to maintain an effective treatment campaign, both for those outside the vaccination scheme as well as for for the minority not protected by BCG. From our experience outside this trial, we think it would be advisable, in BCG campaigns against tuberculosis in areas where leprosy is hyperendemic, to examine children over the age of 5 to exclude leprosy, as BCG can occasionally precipitate violent reactions in leprosy patients.

This was a carefully planned investigation, and it has, in our view, established the early value of BCG against leprosy in Africa. An assessment of its long-term value will depend on the continued observation of those included in the trial.

ACKNOWLEDGEMENTS

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Leprous Myositis—A Histopathological and Electron-microscopic Study

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Microscopic and electron-microscopic examination of biopsy specimens of striated muscle and of the dartos tunica of the scrotum obtained from patients with lepromatous leprosy showed that the changes in leprous lesions of muscle occurred in 3 stages, viz. invasion by and proliferation of *Myco. leprae*, followed by degeneration of the muscle fibres and infiltration by leukocytes, and finally by replacement of the muscle fibres by fibrous tissue. Several lepromatous granulomata were observed in areas around blood vessels in the perimysium.

Mycobacterium leprae was cultured for the first time, though with limited multiplication, by Shepard (1962) in the footpads of mice. Later, Palmer et al. (1965) localized the exact site of multiplication of the organism in the striated muscles of the footpad. It is said (Rees and Weddell, 1968) that within a few hours of injecting the bacilli into the footpads they can be found in the muscle cells. However, in the human patient leprous lesions in the muscle are reported to be infrequent. As far as we know, in the literature there are only 3 papers, 2 describing leprous lesions of striated muscle (Ishihara, 1959; Convit et al., 1960) and one demonstrating the infection in the dartos tunica (Harman, 1968).

In this present paper we describe the histopathological and the electron-microscopic appearance of leprous myositis in both striated and smooth muscles, and point out that the infection of superficially situated smooth-muscle cells is not an uncommon finding in lepromatous leprosy.

MATERIALS AND METHODS

In all, 8 muscle biopsy specimens of lesions from patients with lepromatous leprosy were available for study. Of these, 6 were from the striated muscles in different parts of the body and 2 from the scrotum, including the dartos tunica, the smooth muscle bundles situated just beneath the scrotal skin.

All the biopsy samples were fixed in 10%formalin, processed, blocked in paraffin wax, sectioned at 6μ thickness, and stained with the following stains: haematoxylin and eosin, acidfast stain, Gömöri methanamine silver (GMS) stain, and Masson's trichrome stain. Two of the specimens were stained with Van-Gieson's, periodic-acid-Schiff (PAS), and Bodian stains. Since there had been no previous intention to include an electron-microscopic study only neutral formalin-fixed tissues were available in 2 cases with infection of striated muscle. However, one of the scrotal biopsy samples was fixed in paraformaldehyde. These biopsy specimens were later treated with osmium tetroxide, embedded in araldite, cut in a Cambridge Huxley microtome, and examined under a Philips EM 200 electron-microscope.

FINDINGS

The changes occurring in leprous lesions of the striated muscles were seen in 3 different stages. First, an initial stage of invasion and proliferation of the Myco. leprae inside muscle fibres and tissue histiocytes. Subsequently, the muscle fibres degenerated and were infiltrated by polymorphonuclear leukocytes, lymphocytes, and macrophages; the bacilli then became fragmented and granular. Finally, the destroyed muscle fibres were replaced by fibrous tissue, the macrophages became vacuolated, and the bacilli disappeared completely.

The active lesions present in 2 of the 6 cases studied, showed slight swelling and thickening of the endomysium. Several lepromatous granulomata (Fig. 1) were present in focal areas, around blood vessels in the perimysium. Adjacent muscle fibres were mostly normal, with longitudinal and cross striations well preserved. However, some of the fibres showed marked vacuolation, loss of striations and even necrosis. PAS staining was negative, indicating absence of glycogen. In some areas the sarcolemmal nuclei were clumped together. A few lymphocytes were also seen scattered diffusely in the muscle tissue. Acid-fast stain and GMS stain revealed numerous bacilli inside macrophages and muscle cells (Fig. 2). A few of these were



FIG. 1 Photomicrograph showing striated muscle with a lepromatous granuloma composed of foamy macrophages and round cells (H & E $\times 250$).



Fig. 2

Photomicrograph to show striated muscle fibres replaced by foamy macrophages containing Myco. leprae. The bacilli were found inside muscle cells also (GMS $\times 2000$). rods and a large number were granular organisms.

As the muscle fibres degenerated there was clumping of sarcolemmal nuclei. In some areas these were arranged in rows one behind the other, but in other areas 5 or 6 nuclei were seen in aggregation. The inflammatory granuloma at this stage consisted of a large number of macrophages, plasma cells, lymphocytes, and polymorphonuclear leukocytes the majority of which were eosinophils. The macrophages showed marked vacuolation (Fig. 3). Acid-fast stain and GMS stain revealed only a few organisms, most if not all of which were fragmented and granular. Several microscopical fields had to be searched before granules of acid-fast bacilli could be detected inside macrophages.

During the healing stage the necrosed muscle fibres were gradually replaced by fibrous tissue; the remaining muscle fibres showed well marked



Fig. 3

Photomicrograph of a healing lepromatous granuloma in the striated muscles. Note the collection of vacuolated macrophages and the diffuse fibrosis of the muscle (H & E $\times 250$).



Fig. 4

Photomicrograph showing nerve fibres supplying muscle bundles infiltrated with numerous inflammatory cells (Bodian $\times 2000$).

striation. In the longitudinal section, muscle fibres were interrupted at intervals by focal areas of fibrous tissue, suggesting that the necrosis of muscle fibres perhaps had been focal and patchy. There was diffuse infiltration of the fibrous tissue by lymphocytes, plasma cells, and a few polymorphonuclear leukocytes. The macrophage collections were still present but were markedly vacuolated; acid-fast stain showed no bacilli in them. Bodian stain showed that the nerve fibres supplying the muscle cells were infiltrated with inflammatory cells (Fig. 4).

The 2 biopsy specimens from the dartos muscle of the scrotum were from active lesions. They showed that the muscle bundles were oedematous and swollen and some were obviously vacuolated. There were focal collections of macrophages, lymphocytes, and plasma cells around the muscle bundles (Fig. 5). Some of



FIG. 5 Photomicrograph to show smooth-muscle bundles from dartos tunica infiltrated by lymphocytes and plasma cells (H & E $\times 250$).



FIG. 6 Photomicrograph showing inflammatory reaction around degenerating muscle cells parasitized by $Myco.\ leprae$ (H & E imes 2000).

the muscle cells were destroyed and replaced by hyalinized fibrous tissue. Acid-fast stain showed numerous smooth muscle cells filled with bacilli, most of which were well stained and rod-shaped. Some of the bacilliferous muscle cells showed hardly any degenerative changes and elicited no inflammatory cell reaction, but in many others there were degenerative changes and granulomatous inflammation (Fig 6).

Electron-microscopic findings

The electron-microscopic studies confirmed the findings seen under the light microscope. In the striated muscle lesions the bacilli were present inside tissue histiocytes and muscle fibres. There was also focal necrosis of individual

muscle fibres, which were destroyed by the presence of clusters of bacilli. Cross striations were well preserved in most of the other muscle fibres, even in those adjacent to the granuloma. There was proliferation of satellite cells. The electron-microscopic study of dartos muscle confirmed the intracellular presence of a large number of bacilli inside phagocytic vacuoles in many muscle cells (Fig. 7). Most of the bacilli were rods and were apparently viable. There were a number of mitochondria showing cystic dilatation (Fig. 8). Some muscle cells containing the organisms showed well-marked degenerative changes, with fragmentation and condensation of myofibrils (Fig. 9) and formation of myelin figures.



FIG. 7 Electron micrograph showing clusters of $Myco.\ leprae$ within smooth muscle cells. Note the phagocytic vacuoles in the cells containing the organisms (\times 11,900).



FIG. 8

High magnification electron micrograph showing several Myco. leprae contained in a phagocytic vacuole in a smooth-muscle cell. The mitochondria are vesiculated and the myofibrils are clumped together. Note the cross-section of the bacteria with cytoplasm, cell membrane, and the waxy coat ($\times 46,300$).



F1G. 9

Electron micrograph of a degenerating smooth-muscle cell containing a cluster of Myco. leprae. Note the large phagocytic vacuole almost filling the cell. The myofibrils cannot be identified any longer, but have clumped together into an amorphous electron dense granular material ($\times 28,900$).

DISCUSSION

The common striated muscle lesion in leprosy is neural in origin, following the loss of nerve supply to the muscle. Direct invasion of the striated muscle by lepromatous granuloma has been reported to be extremely uncommon. There may be several reasons for this. Muscular lesions of bacterial origin are rare, because the muscle fibres contract so frequently that microorganisms do not easily settle in muscle tissue and produce lesions, except in unusual circumstances. Further, the metabolites produced in muscle may alter the tissue in such a way as to prevent the growth of these organisms. Of the 6 cases in which granulomata were present in striated muscles, solid forms of *Myco. leprae* were absent in all but 2, and even in these 2 only a few solid bacilli were seen.

In the biopsy specimens from the scrotum large clusters of acid-fast rods were present inside smooth muscle cells. These latter cells degenerated into vacuolated and later necrotic cells. Smooth muscle involvement is not an uncommon finding. In skin samples from lepromatous patients it is not unusual to find the fibres of the arrectores pilorum muscle parasitized extensively by Myco. leprae and these organisms are also seen in the smooth muscles of blood vessels in the skin and subcutaneous tissue (C. K. Job, personal observation). Smooth muscle may have a composition which is different from that of striated muscles and

which is conducive to bacillary growth, or the smooth-muscle cells are present in an environment conducive to the growth of the bacilli. Myco. leprae have never been detected in the smooth muscle of the gastro-intestinal tract or other deeper structures. Therefore, it is reasonable to deduce that it is the environmental factors that make the difference. One of us (C.K.J.) believes that the lowered temperature in the subcutaneous smooth-muscle cells in the scrotum and skin is an important factor for the growth of the organisms in these sites. Smoothmuscle cells have a long life-span and their physical environment in the skin and scrotum compares well with the Schwann cells in the cutaneous peripheral nerves and therefore they also offer suitable conditions for Myco. leprae to multiply. We have every reason to believe that bacilli proliferate as much in the smooth-muscle cells at these sites as in Schwann cells. Therefore, it is reasonable to say that Schwann cells need not necessarily be the main target cells, as is thought at present. Any cell that has a long life-span and has an environment conducive to the growth of the organism will be parasitized and colonized by Myco. leprae.

The infection is carried to the muscle either through direct extension from the skin or through the blood stream. The spread along the perimysium may give the impression that the infection might have spread from the contiguous skin to the muscle along the muscle spaces. However, the special predilection of the granuloma for a site around blood vessels and the focal and selective destruction of muscle fibres following the granulomatous inflammation suggest that the bacteria are carried into the muscle bundles via the blood stream.

SUMMARY

In this study of 8 muscle biopsy specimens from lepromatous patients, of which 6 were from striated muscles and 2 from the dartos tunica of the scrotum, lepromatous granuloma consisting of macrophages containing Mycobacterium leprae, lymphocytes, and plasma cells were present in all of them. The bacilli were seen to grow in the muscle cells also, bringing about their degeneration and necrosis, followed usually by granulomatous inflammation. These findings were confirmed by electron-microscopic studies. Colonies of solid bacilli were demonstrated inside muscle cells. It is pointed out that in lepromatous leprosy infection of smooth-muscle cells is not an uncommon finding and that Schwann cells need not necessarily be the main target cells of Myco. leprae, which may grow in any cell having a long life-span and an environment conducive to the growth of the organisms.

ACKNOWLEDGEMENTS

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Sensitivity Testing as a Means of Differentiating the Various Forms of Leprosy Found in Nigeria

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In this study, tests of cutaneous sensation carried out with nylon threads on a group of healthy Nigerian subjects and 2 groups of leprosy patients have shown that the patients with lepromatous leprosy manifested increased cutaneous sensitivity, and further that a progressively increasing number of positive responses indicated lepromatous reactivation.

Danielssen and Boeck, in 1848, and Virchow, in 1864, described the alterations in cutaneous sensation and the involvement of the peripheral nervous system in leprosy. Since that time more and more evidence has accumulated to show that the peripheral sensory nerves of the skin are destroyed in tuberculoid leprosy and partially destroyed in borderline or dimorphous leprosy, while recently an increase in the number of small nerve fibres in the dermis at certain stages of lepromatous leprosy has been demonstrated.

The object of this paper is to describe a method of testing one aspect of cutaneous sensation in a roughly quantitative way, to show the pattern of responses to this test in different parts of the body in a series of normal Nigerian volunteer subjects, and to contrast these findings with those in a series of leprosy patients from the same racial and economic background. It is hoped to show that information about the type of leprosy, the progress under treatment, and any reactivation of the disease may be obtained by means of this simple test, and that the test may be of value where laboratory facilities are not easily available.

MATERIALS AND METHODS

The testing stimulators used are illustrated in Fig. 1. Six nylon threads of graded thickness are mounted in holders as shown, monofilament nylon sutures of thickness No. I to No. VI being used. Fig. 2 illustrates the skin areas tested



The stimulator.

in the healthy Nigerian volunteers. This group consisted of 15 men attending a course for dispensary attendants at Kaduna in Northern Nigeria, 7 women attending a child-welfare clinic in Katsina Province of Northern Nigeria, and 5 schoolboys from the junior primary school at Rimi, also in Katsina Province. All 27 subjects had been medically examined and found free of disease, and none had any family or house contact with leprosy.

The 16 leprosy patients studied can be divided into 2 groups: (A) 4 patients all from Katsina Province, all untreated when first investigated, and all re-investigated after one year and again after 2 years of regular out-



Skin areas tested in normal subjects.

patient treatment with dapsone. At each investigation biopsy specimens of the tested skin areas were taken and examined for the presence of mycobacteria and the distribution of nerve fibres; and (B) 12 patients taken from among those attending out-patient treatment centres in Katsina Province. All 12 were tested with lepromin and all were examined by means of skin smears for the presence of mycobacteria.

In the normal series the sensitivity test was carried out as follows. A skin area 2.5 cm (1 in.) in diameter was selected and lightly shaved; where possible corresponding areas on the right and left sides of the body were similarly prepared. The volunteer was shown the stimulators, reassured that no painful sensation would result from their application, and told to indicate with one finger wherever he felt they had touched him. Next he was blindfolded and each of the 6 nylon stimulators was applied 3 times at random to the shaved area; from time to time the stimulator was applied to the corresponding area on the opposite side of the body. Each stimulator was delivered at right angles, allowed to bend to the same degree,

kept in contact for the same length of time, and not dragged over the skin surface. The results were recorded as "felt" or "not felt"; minor degrees of misreference were recorded as "felt" and gross misreference or no response as "not felt". Failure to recognize stimuli delivered to the opposite side of the body invalidated the test.

In the leprosy patients with circumscribed skin lesions the test was carried out at 3 sites, namely, on the skin of the lesion, on the normal skin beyond the leprosy lesion on the same side of the body, and on the normal skin over a comparable area on the opposite side of the body. In those with generalized lepromatous leprosy the reaction of the infiltrated skin of a particular area on the right side of the body was compared with that on a similar area on the left side.

TABLE 1

Responses of 27 subjects (15 males, 7 females, 5 children) to stimuli with nylon thread

Site stimulated			Thread number						
			I	Π	Ш	IV	V	VI	
Brow			75	м	М	М	м	М	
Cheek			79	М	М	М	М	М	
Chin			77	М	М	М	Μ	М	
Anterior nec	k		70	М	М	М	М	М	
Below clavic	le		63	79	М	Μ	М	.М	
Over lower r	ibs		53	75	М	М	Μ	М	
Front of thig	gh		57	75	М	М	Μ	М	
Above knee	• •		54	76	80	м	М	М	
Front of tibi	а.,		43	60	65	Μ	М	М	
Dorsum of fo	oot		57	76	77	М	М	М	
Front of upper arm			58	68	М	М	М	М	
Flexor forea	rm		42	72	М	М	М	Μ	
Back of upper arm		46	74	М	М	М	М		
Elbow			0	- 0	14	46	80	М	
Back of fore	arm		78	М	Μ	Μ	М	М	
Back of hand	d		39	68	М	Μ	М	М	
Back of thig	h		60	72	М	М	М	М	
Calf			32	57	79	М	М	М	
Over heel			28	51	77	Μ	М	Μ	
Ear			Μ	М	Μ	М	М	М	
Posterior neo	ek		53	77	М	М	М	Μ	
Scapula regi	on		60	76	М	М	М	М	
Lumbar regi	on		54	73	М	М	М	М	
Back of knee	э.,		М	М	М	М	М	М	

M, maximum response by all subjects.

Figures indicate number of responses to 81 stimuli.

RESULTS

The results of the test in the 27 normal volunteers are shown in Table 1. Each stimulator was applied 3 times to each area in each of the 27 volunteers. The letter M represents 81 responses to 81 stimuli, i.e. the maximum possible. The figure 75 in Column I indicates that 75 responses were obtained to stimulator No. I out of a total of 81 stimulations.

A review of these results as a whole reveals that the face, ears and back of the knee were the most responsive sites, while the skin of the legs and particularly of the elbow was the least responsive.

The 4 leprosy patients in Group A were: (1) a woman with a single tuberculoid lesion, a positive lepromin test result, and a patch on the flexor surface of the forearm; (2) a man with

borderline lesions, a positive lepromin test, and multiple patches on the forearm; (3) an older man with possibly lepromatous macules, a negative lepromin test, and multiple small macules on the forearm; and (4) a young man with advanced lepromatous leprosy, a negative lepromin test result, and generalized lepromatous infiltration of the skin of the whole body.

Fig 3 summarizes the results of the sensory testing in these 4 patients at 3 sites, namely, (a) the skin of the forearm lesion, (b) the skin beyond the lesion, and (c) the skin of the opposite forearm.

The first patient illustrates the pattern of responses obtained in tuberculoid leprosy. The lesion is initially anaesthetic while the unaffected skin on both forearms gives responses that are within normal limits. As the result of



a,Infiltrated skin right forearm; b, infiltrated skin left forearm.

FIG. 3 A breakdown of normal patterns of response in the 3 groups *not* included. treatment, however, the lesion gradually becomes more responsive while the normal skin remains unchanged. Patient No. 2 at the first examination shows anaesthesia of the lesion, but a greater number of responses to stimuli on the opposite forearm compared with the control series. However, with treatment the number of responses from the lesion increases and the pattern from the skin of both forearms returns to normal. In the 3rd and 4th patients the skin of both forearms consistently responds to all stimuli and this pattern is in no way altered by treatment.

In Group B, 8 of the 12 patients showed a general lepromatous infiltration of the skin of the whole body. In spite of variable periods of treatment, mycobacteria could still be found in skin smears. All 8 failed to respond to lepromin. In all 8 patients the same increase in the number of responses to stimuli as compared with the normal series was observed even though the skin areas tested ranged all over the body.

CONCLUSION

It is concluded that an increased number of responses compared with the normal established pattern indicates the presence of lepromatous leprosy, and that a progressively increasing number is an indication of lepromatous activation.

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G 30 320 or B 663—Lampren (Geigy)*

A Working Party held at the Royal Garden Hotel London, September 1968

Chairman

Dr. M. F. R. Waters

Dr. R. H. Gosling (Geigy, Macclesfield) welcomed the participants and introduced the Chairman

1. ANTIBACTERIAL ACTION OF G 30 320 IN LEPROMATOUS LEPROSY Effect on untreated lepromatous patients, with particular reference to bacteriology, considering the morphological index and then the bacterial index

MORPHOLOGICAL INDEX (M.I.)

CHAIRMAN: The morphology of Mycobacterium leprae is a controversial subject. Many leprologists believe, and I admit to being one of them, that fragmented bacilli are dead and that the majority of solid-staining bacilli are alive. Others remain unconvinced. Be that as it may, it is undisputed that leprosy bacilli become fragmented under effective anti-leprosy treatment. It was noticed from the first introduction of effective chemotherapy, and reported in 1946 by some of the giants of leprology (such as the late President of the International Leprosy Association, Dr. Fernandez, and our honorary Vice-President, Dr. Muir), that bacilli of patients under sulphone treatment soon become fragmented; and this fact was mentioned in the report of the Panel on Therapy at the 1948 Congress in Havana.

I now ask for your experience with the morphological index, which is defined as the percentage of solid-staining bacilli smears being taken at one time from several sites, and an average calculated. Before beginning, I would particularly like to welcome Dr. Vincent Barry, who discovered G 30 320 in his laboratories in Dublin, and Dr. Stanley Browne, who was the first person to use it clinically in leprosy. It seems appropriate to call on Dr. Browne to make the first contribution.

DR. S. G. BROWNE (LONDON): For many years we have used the morphological index (M.I.) as the most sensitive indication of the mycobactericidal activity of a drug. In early work with G 30 320 we habitually used the index as calculated from 8 body sites (including 2 from the septal mucosa of the nose), examined and stained by a uniform technique and dealt with by the same very experienced technician. Definite solid-staining and deeply staining bacillary forms were counted as normal; all other recognizable bacillary forms not deeply or uniformly staining were regarded as abnormal. The patients were all untreated. The average initial height of the morphological index was 54%, which may seem somewhat high to workers in other countries, but in the deeply-pigmented African with a very high turnover of epithelium and of nasal mucosal epithelium, this is not an unusual figure. The range was from 0 to 100, but in the great majority of patients the index would fall between 30 and 60%. In untreated patients with severe lepromatous leprosy under G 30 320 therapy, the index fell to zero in an average period of 30 to 32 weeks. The fall was regular, and occurred at all sites, but was sometimes less rapid in the nose than elsewhere. The rate of fall in pure lepromatous disease did not depend

^{*}*Editorial note:* Some speakers referred to G 30 320 and others to B 663; for the sake of uniformity G 30 320 is used in this report. The chemical formula and structure of Lampren are given on page 47.

upon the initial height of the morphological index, or on the dose level of G 30 320 given. There was a transient rise in the M.I. from time to time of no prognostic significance; it occurred at one, at several sites, or at all sites, especially in the nasal mucosa. The bacilli were still sensitive to the drug, bacteriological progress being resumed on continued therapy.

There is no real difference between a dapsone regime and G 30 320 as regards the time taken to render lepromatous patients non-contagious.

DR. J. H. S. PETTIT (KUALA LUMPUR, MALAYSIA): I do not have much to add to the papers that are summarized in our book of abstracts.* As far as the morphological index is concerned, the fall is exactly comparable in sulphone-resistant and ordinary cases. You will see that it is steep at first, then much slower, and that the transient rise mentioned by Dr. Browne also appears in one or two of our cases. We do not use nasal smears at Sungei Buloh; all our smears are taken from other parts of the skin, but even then there is an occasional rise, as seen in 2 of the cases between the third and the sixth months.

DR. J. M. H. PEARSON (SUNGEI BULOH, MALAYA): The curves in Fig. 1 are averages for 4 different groups of 6 to 10 patients each, and the fall in the M.I. was plotted from smears taken every 6 weeks during the initial 6 months of treatment. Line A represents 6 cases on G 30 320, 100 mg twice weekly. Line B represents 100 mg daily. That was in a group of patients resistant to dapsone treatment. Lines C and D represent patients treated with G 30 320, 100 mg 3 times a day; one group is of previously untreated lepromatous cases, the other of cases with proved sulphone resistance. Line E represents the fall in a group of patients treated with dapsone, 50 mg twice weekly. This confirms what Dr. Browne said, that judged by fall in the M.I., patients on G 30 320 in the dosage we have used respond comparably to those treated with dapsone.



Fig. 1 Fall in M.I. in the first 6 months of treatment with G 30 320.

DR. F. M. J. H. IMKAMP (KABWE, ZAMBIA): I have a few patients in a drug trial who were corticosteroid-dependent for some years; their M.I. was still high and they responded to G 30 320 treatment, and the M.I. came down. One lepromatous patient was given a loading dose of 300 mg for 3 weeks and then 100 mg a week; his M.I. responded very favourably.

DR. B. L. LEIKER (AMSTERDAM): I have treated 42 patients, but all had received previous treatment. I have divided this group up into: (1) uncomplicated cases (2) cases with previous serious reactions. We assessed bacteriological progress on serial biopsies taken every 3 months from the same lesion. Reduction of infiltration in the first 9 months of treatment is not marked. Some of these patients have been treated now for up to $2\frac{1}{2}$ years, and in the second year of treatment, the changes become more marked. Bacteriological progress is of the same order as with dapsone. The bacillary index decreased in patients on average at a rate comparable with that in standard dapsone treatment-a decrease of about one unit per annum.

^{*}The abstracts were available only at the meeting. A list of published reports on Lampren is available on request from the Geigy Company.

CHAIRMAN: It is generally accepted that determination of a morphological index on bacilli in sections is more difficult than in smears, and I am very interested to see your results.

DR. B. L. LEIKER (AMSTERDAM): I found that the changes in smears were comparable with those in sections.

CHAIRMAN: I should point out that figures for the M.I. and the methods of assessing a solid-staining bacillus differ in different parts of the world. I understand that a W.H.O. working party will be discussing this very point after the Congress. However, even if the figures differ we can compare the shape of curves.

I want to show one curve (to be published) obtained from 8 histologically proven lepromatous cases who were previously untreated and had no dapsone in their urine. These patients received 100 mg G 30 320 twice a week, a much smaller dosage than that given to the majority of patients whose M.I. curves you have seen. Exactly the same shape of curve is obtained and, after $4\frac{1}{2}$ months' treatment, very few solid-staining bacilli are left in the smears.

The evidence presented here shows that the M.I. falls rapidly in untreated lepromatous cases so that within a few months of the start of treatment there are very few solid-staining bacilli left. The rate of fall is comparable to that obtained with standard sulphone treatment, although no controlled comparisons have been presented this afternoon. That is my one criticism of this work.

BACTERIAL INDEX (B.I.) Bacteriological index (B.I.) of Myco. leprae (Ridley's logarithmic scale)

1+: at least
1 bacillus in every 100 microscope fields
2+: at least
1 bacillus in every 10 microscope fields
3+: at least
4+: at least
10 bacilli in every microscope field
5+: at least
100 bacilli in every microscope field
6+: at least
1000 bacilli in every microscope field

The B.I. is calculated from the examination of 6 to 8 stained smears under the +100 oil immersion objective.

CHAIRMAN: The bacterial index is the old

standard method for assessing bacterial improvement. However, some prefer the 0 to 4 plus system, while others use Ridley's logarithmic index (0 to 6 plus). I would ask contributors to state which system they used.

DR. S. G. BROWNE: Our definition of the B.I. is the arithmetical average of the collated indices from a standard number of sites (8), the smears being taken by a standard technique. We have used the old Dharmendra notation from 0 to 4, which is roughly geometrical and roughly comparable to Ridley's 0 to 6. The rate of fall in untreated patients with lepromatous leprosy varied tremendously. Some patients, especially those with long-standing lepromatous disease, seem unable easily to get rid of acid-fast material from their skin and nasal mucosa. The index varies also with the amount of acid-fast material there is to be removed, that is to say, with the actual bulk of the subcutaneous granuloma. The average rate of fall of the B.I. in one series was up to 34% in 6 months, 46%in 12 months. There was no apparent relation between the high doses given in one series, 300 mg/day, and the lower doses of 100 mg/day or 100 mg every other day given in another. Nor was there any significant difference between patients who had a loading dose of 300 mg/day for 3 weeks followed by a standard dose of 100 mg/day, and others who had no loading dose.

Can the B.I. be reduced by increasing the dose of G 30 320? It is possible, but in my opinion very unlikely, because the mechanisms of killing mycobacteria are different from those for removal of effete acid-fast material from the tissue. Bacilli-filled macrophages must still be induced to leave the sites where they are congregated. We have experience of some examples of transient rises in the B.I.; various explanations are given, such as the vagaries of smear-taking, the existence of small pockets of morphologically normal bacilli, semi-encapsulated material in fibrous tissue, and the sudden recrudescence of bacillary activity in a localized area. The hormonal disturbances of parturition and pregnancy may also account for a transient nonsignificant rise in the B.I.

DR. R. C. HASTINGS (CARVILLE, LOUISIANA): Our experience has roughly corresponded with Dr. Browne's. The B.I. as determined from skin scrapings falls quite adequately with G 30 320.

DR. GRACE WARREN (HONG KONG): I have been using G 30 320 mainly in the treatment of Chinese patients with chronic lepra reaction. This is usually long-term erythema nodosum leprosum (ENL), with high fever, arthritis, neuritis and iritis. To these patients we gave G 30 320, in most cases after every other available anti-leprosy drug and many other treatments had been tried, including prednisolone in some cases.

The first patient to whom we gave G 30 320 was a girl (No. 1486) who had been bed-ridden for almost 12 months, and whose bacteriological index had made no progress for 4 years. A number of sulphones were tried, and at the end of 1966 sulphoxone was given, then stopped and G 30 320 started. 300 mg/week was continued for 6 months during which time her B.I. fell from 3.8 to 2.3. She still continued to have some lepra reaction until we increased the dose to 600 mg/week, which controlled it completely. The B.I. has continued to fall through at a slightly slower rate, but compared with her previous state this is a very dramatic fall.

By the time that a further supply of G 30 320 arrived, we had many patients asking for the new drug. In a male patient (No. 1340) who started on G 30 320 in the middle of 1967, the B.I. fall continued at about the same rate that we had been achieving with injected thiambutosine, but his general condition improved dramatically. Another patient (No. 1661) had chronic reaction for 2 years with no improvement in the B.I. Once she commenced G 30 320, the B.I. fell dramatically; reaction was controlled by 600 mg/week, though not by 300 mg.

Another patient (No. 1447) had made slow progress over a period of 6 years. On G 30 320, the fall in B.I. was very dramatic for the first 6 months, but then stopped despite continued therapy. We have seen this in a number of patients, but have no explanation for it yet. The reverse may be seen (No. 1333). For the first 6 months on G 30 320, the general condition may improve without the B.I. showing any improvement; then there may be a rapid fall. The dose needed to control reaction has varied from one patient to another. There seems to be some relation between the rate of B.I. fall and the amount of drug given, but I have not been able to determine it properly yet.

CHAIRMAN: You recently published a paper on the rate of B.I. fall in patients on standard sulphone treatment. How does this compare with the fall on G 30 320?

DR. WARREN: The standard rate of fall of B.I. in Chinese patients on dapsone therapy is 1 unit/annum. It falls in annual steps from 4 to 3 to 2 to 1. After that you cannot predict how Chinese patients will react. The fall in B.I. in patients on G 30 320 was, in the 12 months under consideration, usually equal to or greater than the fall expected in patients receiving dapsone. In most cases, the fall was much greater than that for the same patient in the previous control period.

CHAIRMAN: Having many Chinese patients myself, I quite agree that it is difficult to predict the B.I. fall in the lower range.

DR. E. F. SCHULZ (PRETORIA, SOUTH AFRICA): Although we have not treated any patients with G 30 320 alone, and all our patients had dapsone before we started the trial, we attempted to establish whether the addition of G 30 320 to dapsone could increase the rate of fall in the bacterial index.

We have had 2 groups of patients: one on dapsone alone, and the other on 100 mg G 30 320 daily plus dapsone. After 18 months there was no difference in the bacteriological index between these 2 groups. There was a marked difference in the incidence in reactions, but that can be discussed later.

DR. A. KARAT (KARIGIRI, INDIA): I would like to ask 3 questions. One is to Dr. Browne. He stated that in 12 months he expects a bacterial clearance of 34 to 46%. This is very unusual in our experience. We use Ridley's scale, and make smears from 8 sites. Second, I noticed in the previous discussion that both he and Dr. Pettit emphasized a transient rise of morphological index. Was there any change in the B.I. at this time? Was there any clinicially recognizable change in the lesion when the morphological index went up? Third, in our experience, the rate of clearance of bacilli in lepromatous patients is somewhat proportionate to the initial bacterial index—the higher the initial index, the greater the drop in the first 12 to 24 months. In other words, whereas I normally expect a change in Ridley's index of 1/year, just as Dr. Warren has described, clearance is quicker in those with a larger number of bacilli until they attain between 2 and 3.

DR. BROWNE: I agree that by south-east Indian standards, these figures may seem unusual. On Dharmendra's notation, the fall was from between 4 and 3.5 to between 3 and 2.8, which would be reflected by a slightly different rate on Ridley's scale. There was no change in the clinical condition suggestive of an increase in the morphological index at the time that this occurred, except that from time to time small cutaneous papillary elevations appeared, replete with morphologically normal bacilli, confirmed histologically and apparently arising in an umbrella-shaped fashion from a focus in the cuticular nerve tissue. The higher the original index, the greater the rate of fall initially under G 30 320, under dapsone or any other therapy. I believe that this finding may be more marked the further east one goes from central Africa.

DR. J. PETTIT: The transient M.I. rise found in some cases is not important. It is not reflected in the B.I., because the M.I. rise usually takes place about the third to fifth month, when there has not been enough time for a significant change in a B.I. with a logarithmic index.

PROF. GATTI (BUENOS AIRES): As far as the B.I. is concerned, my experience is that the fall during treatment with G 30 320 is comparable with that on dapsone, and more rapid than with longacting sulphonamides or thiambutosine. DR. RODRIGUEZ (MEXICO): In Mexico many untreated patients show a fall in the M.I. and this should be borne in mind when considering the effect of drug treatment.

DR. BROWNE: My early figures were based upon several series in Nigeria. We have some patients on G 30 320 today in this country whose B.I. has shown practically no change after 6, 9 and even 12 months. We are up against the problem of getting rid of unpalatable mycobacterial debris, and this apparently is not affected by any drug at present given for leprosy.

We also have noted variations in the M.I. in patients not under treatment, and therefore advocate the taking of fortnightly smears on at least 3 occasions before the beginning of any controlled therapy. When a patient is admitted to a leprosy settlement, the regular life, the good diet, and the restful atmosphere may all contribute in some unexplained way to a change in the M.I. I would, in contrast to Dr. Leiker's proposal for a 3-monthly assessment of such indices on biopsy findings, advocate a monthly assessment from 8 sites. In that way much better understanding of the average bacteriological activity in skin and nasal mucosa would be obtained.

DR. PEARSON: Fig. 2 shows average changes in the B.I. (Ridley's scale) in patients who had



previously been untreated or who were sulphone resistant, and therefore at the time of starting treatment with G 30 320 were in effect untreated. The figures on the curve represent the number of patients included on each occasion. The rates of fall appear to be different on different doses of G 30 320, but the number of cases is small and it is possible that there are no significant differences. The rates of fall appear to be comparable with those found during routine sulphone treatment.

DR. KARAT: I wish to underline what Dr. Browne has said. We have done some work on twice-monthly morphological indices, but for some unexplained reason they fluctuate significantly even when patients are not on any specific treatment, and I think the point is well taken. In our experience the clearance of bacilli is in some measure related to the dose of dapsone in lepromatous leprosy patients.

CHAIRMAN: We have had clear evidence that the B.I. does fall under G 30 320 treatment. I gain the impression that speakers who discussed B.I's from previously untreated patients receiving G 30 320 as their first drug reported a rate of fall comparable to that obtained with dapsone, although again no fully controlled trials were presented. The B.I. charts from Dr. Warren's patients who had previously received a number of different drugs and whose bacterial indices had become stationary showed a very definite fall.

CONTROLLED TRIALS

CHAIRMAN: If anybody has any provisional results from a controlled trial, I should be most grateful if they could be presented now.

DR. KARAT: I think the terms "controlled trials" and "preliminary results" with G 30 320 are open to criticism for the following reason. In our group at the end of 30 days the trial ceased to be "controlled" if the patients were receiving 600 mg or more of G 30 320/week, and therefore the results I gave are classified as "controlled", but in fact after one month they have become "randomized" trials rather than "controlled" trials. With that proviso, I would add that among the 17 patients we have been following up for the last few months, the changes in the 2 groups receiving 600 mg G 30 320 and 600 mg dapsone are identical.

DR. RUSSELL (NEW GUINEA): We began to study G 30 320 at a leprosarium in New Guinea and attempted controlled trials. We were defeated because the rate of admission of completely untreated new patients was too slow for us to select adequate numbers. We also ran into difficulties of fair and honest matching of patients to put into these 2 control groups. We have treated in all 31 patients, starting with 7 on dapsone and 7 on G 30 320 alone. We determined the bacteriological index (Ridley) using a series of 6 smears, including nasal. Two of our patients on dapsone very rapidly became negative and the rate of fall was in fact more rapid than with G 30 320.

After an average of 20 months' treatment, we had 4 completely negative smears, which compares with similar claims for the M.I. With the sulphones in the same period (of roughly 20 months) we found 2 negative smears out of 7. In the first 3 months we observed a transient rise in index in the smears of several patients; then gradually the smears began to alter.

We have now abandoned any attempt at a controlled trial and are treating a greater number of patients in chronic reaction—comparable with Dr. Warren's—who have had a series of drugs, including very long periods on steroids. We have tried to concentrate help on this type of problem patient. In some institutions 30% of our patients are in reaction. Lepra reaction improved in 16 patients without any doubt. We had 11 failures, but some of these responded later. We are still pursuing this.

CHAIRMAN: This report illustrates the difficulties of performing controlled clinical trials in leprosy. I wonder if Dr. Leiker has any information on controlled trials.

DR. LEIKER: Yes, we have a series of comparable data, but not matched pairs of patients. In a reliable control group the results were practically the same as with G 30 320.

HISTOLOGY

PROF. GATTI: After 6 months' treatment with G 30 320, there was a decrease of acid-fast material and fewer Virchow cells in both borderline and lepromatous cases, with some increased fibrosis and mild pigmentation in the basal layer of the skin in lepromatous cases. In one indeterminate case the neuritic infiltrate practically disappeared in 6 months.

DR. R. C. HASTINGS: We have used G 30 320 in various combinations on 9 patients for from 12 to about 38 months. We compared the Ridley biopsy index in 3 groups, each of 3 patients, on G 30 320 plus INH (isoniazid), G 30 320 alone, and G 30 320 plus dapsone. Among our patients 2 are sulphone resistant (one confirmed in the mouse foot-pad) and 5 had been treated for chronic erythema nodosum leprosum. We expressed the biopsy index as a percentage of the pre-treatment value.

We were a little disappointed in the combination of G 30 320 (200 mg daily) and INH (300 mg daily). After some 30 months, the index was 63% of the original biopsy index. With G 30 320 alone, the index fell to about 50% of the its pre-treatment value. We compared results with the recorded values of a 25 to 30% drop every 6 months in the biopsy index reported for sulphones and our results did not seem to be quite as good.

CHAIRMAN: There are 2 aspects to histological studies. One is the histological changes under treatment, and the other the assessment of the biopsy index, and its rate of fall under treatment. I should like to confine discussion to the rate of change or rate of fall of the biopsy index.

DR. J. PETTIT: I have little to add to the published statements. The fall in biopsy index in a series of 6 cases of lepromatous leprosy (2 borderline) was 40% in a 5-month period, the assessments being made according to the biopsy index as amended by Dr. Ridley.

PROF. GATTI: The biopsy index has been studied in 13 patients and we obtained results similar to those of Dr. Pettit, the fall being 37% in 6 months.

DR. N. C. DA SILVA (RIO DE JANEIRO): I would

like to emphasize the importance of histological and histochemical findings in drug trials. We have developed a technique based on differential staining for lipids with a yellow dye which we prepared from the pollen of dahlias. After treatment with G 30 320 there was no specific staining of lipid, but a diffuse penetration of the epithelioid cells in tuberculoid lesions. In lepromatous cases there was also diffuse penetration of lepra cells and epithelial cells with the stain; the section took on a golden tone and we saw some orange crystals which sometimes fluoresced.

PROF. E. AZULAY (RIO DE JANEIRO): We published a paper about 15 years ago on the effect of dapsone on the histopathology of lepromatous leprosy. At that time we did not have the bacteriological or morphological indices, but we observed Virchow cells completely devoid of all bacilli after 3 to 4 years of dapsone treatment. The infiltrates were less marked but we sometimes found 2, 3 or 4 Virchow cells still present without any bacilli at all. In my opinion the Virchow cell is the last to disappear, at least with dapsone treatment.

CHAIRMAN: We have had only a small number of contributions on histology, but by reference to published papers and so on, we know that G 30 320 does cause a fall in the biopsy index. On the short term and in non-controlled trials, this rate of fall seems to be somewhat similar to that with dapsone.

CLINICAL RESULTS

CHAIRMAN: We will now discuss clinical appearances and the influence of G 30 320 on leprosy lesions at different sites, again restricting ourselves to previously untreated lepromatous patients. We start with skin lesions and then deal with other structures, such as nerves, eyes and viscera.

DR. BROWNE: In the various forms of untreated lepromatous leprosy characterized by pre-lepromatous macules, lepromatous macules, nodules, or diffuse infiltration, there is a marked regression of all lesions, including re-pigmentation of the hypopigmented pre-lepromatous and lepromatous macules, and flattening of the raised lesions—papules, nodules, plaques and diffuse papular infiltration. The hyperpigmentation in these lesions is extremely variable, not only in deeply pigmented but also in lightly pigmented Caucasian skin. In some patients the difference in pigmentation (ruddiness and hyperpigmentation) is scarcely noticeable, even though 100 mg/day of the drug is given. In others 50 mg/day will produce a most noticeable ruddiness followed by slatey-grey hyperpigmentation.

To particularize on the raised lesions of leprosy, the small highly bacilliferous papules tend to flatten rapidly, losing their pinkish and yellowish coloration and gradually merging into the surrounding, apparently normal skin. They leave small scars, shiny and lightly striated, frequently hyperpigmented for several months while treatment with G 30 320 is continuing and even after it has stopped.

The flattening of nodules on ear lobes and at other sites of predilection on the face proceeds more slowly, depending upon the depth of granulomatous tissue to be acted upon by the drug and on the fibrosis following its specific mycobactericidal action. In other words, the nodules take much longer to flatten than do the highly bacilliferous and oedematous papillary elevations in the skin. When the nodules do flatten and disappear, their place is taken by puckered scars, the degree of puckering depending upon the initial depth of the granulomatous infiltration of the dermis. The plaques and larger areas will repigment and may even hyperpigment, often after a localizing of the ruddiness which is apparent in variable degree. The larger papillary areas may take a long time to flatten; in other words, where there has been a high initial degree of infiltration in the dermis, the fibrosis is a slow continuing process not greatly accelerated by G 30 320 or by any other anti-leprosy drug.

In previously treated lepromatous leprosy patients with a high degree of dermal fibrosis, absorption of the granuloma is very slow and may take several years; during that time the hyperpigmentation due to G 30 320 will persist. This may be socially unacceptable to groups of patients with lightly-hued Caucasian skin, but those who have been treated for persistent exacerbation regard it a small price to pay for steady amelioration of their clinical condition and a general sense of well-being.

PROF. GATTI: I would confirm what Dr. Browne has just said. There is a flattening of lesions beginning between the first and the third month of G 30 320 treatment. The lesions become less infiltrated and then pigmented. The nodules are flattened, atrophic and wrinkled. All this is more evident at the sixth month.

DR. J. TOLENTINO (CEBU CITY, PHILIPPINES): I should like to tell you about a patient with very advanced lepromatous leprosy, who had huge lepromatous nodules all over the body and had been receiving dapsone for a long time, but steadily deteriorated. He was then given thiambutosine without any improvement. Finally, G 30 320 was tried, and the improvement was very remarkable, so much so that in one year about half the nodules had subsided and many of them became flat.

CHAIRMAN: This was a patient with presumed sulphone resistance.

DR. IMKAMP: One of my patients with lepromatous leprosy was thiambutosine resistant. After about 12 months' treatment with the injectable form, the M.I. actually rose; she was also prone to ENL. After G 30 320 was started, she had one mild ENL reaction, which responded to an increase in dosage. The M.I. is now zero. The disease is clinically inactive, and she is employed on the wards.

DR. SCHULZ: I have treated a patient for 18 months with a combination of G 30 320 and dapsone, one of a controlled group of 16 patients, with 15 patients on dapsone alone. He had diffuse lepromatous leprosy, with nodules; after one year the marked flattening of the nodules and the pigmentation are well seen. I cite this case to plead for controlled trials. This patient did remarkably well. After 18 months there was no significant difference in the improvement in the clinical appearance of the 2 groups. CHAIRMAN: I fully support your plea for controlled trials. As, in particular, the huge trials by the Leonard Wood Memorial group in the early 1950's showed us, the only way to assess any drug accurately is by a controlled clinical trial.

DR. E. KARURU (FIJI): I have observed the return of sweating in tuberculoid and some other types of leprosy after treating with G 30 320.

Ocular Effects

DR. GRACE WARREN: Of the 48 patients that we have treated with G 30 320 so far, about 35 had previously had eye complications, mostly iritis. Most of them had no recurrence of iritis after 3 or 4 months on G 30 320. At the beginning, since I was not checking the eyes regularly, the condition may have come under control sooner, but there was only one patient—a girl who had been on prednisolone—whose eye lesions remained active for about 6 months. In the others, the iritis was brought completely under control within 3 or 4 months of commencing G 30 320.

DR. IMKAMP: All our patients on G 30 320 were examined with the slit lamp by an experienced ophthalmologist, and no active ocular disease or abnormal pigmentation was found.

DR. HASTINGS: Dr. Margaret Brand has examined my patients periodically with the slit lamp, and there seems to be general improvement in both the bacteriological and the reactional states in the eyes. There may be circumcorneal pigmentation which mimics an iritis on superficial examination.

DR. BROWNE: I should like to emphasize the deposition of micro-crystals in the cornea, particularly in the meridional region in the African Bantu, who is subject to various lesions in that region; this finding is of no prognostic significance and there is no disturbance of ocular function. I would confirm the improvement in acute iritis and iridocyclitis during administration of G 30 320 and the general amelioration in the patient's condition as

showing the activity of the drug. It has a non-specific effect in reducing the duration and severity of acute iritis.

Visceral Changes

DR. KARAT: We find that in patients in reaction any lymphadenopathy tends to regress after between 10 and 14 weeks when they are given doses of 300 mg G 30 320 daily. Second, for some unexplained reason, red cells appear in the urine between the fourth and the eighth week, and tend to disappear between the twelfth and eighteenth weeks. We have studied a few renal biopsies, but the findings are preliminary and we cannot yet discuss them. Third, there has been a change in creatinine clearance in patients on G 30 320 as compared with those on prednisolone. Fourth, the improvement in blood findings over a period of 4 months has not been impressive, though the changes in albumin levels are somewhat encouraging. Lastly, I was very impressed by the subsidence of unexplained bilateral pitting oedema both in untreated lepromatous leprosy and in the reacting group, while the patients were having G 30 320. I infer that this may have something to do with the alteration in creatinine clearance that I have already referred to.

PROF. GATTI: I should like to mention the lesions seen in the mucosa of the throat and larynx. These include ulcerative lesions in the throat, including the uvula and tonsils, and congestion. After 6 months' treatment with G 30 320, intense fibrosis of the lesions could be seen and the ulcers disappeared. One patient complained of dyspnoea and fatigue, and thought he had asthma. He was treated with 300 mg G 30 320/day, and the dose was later raised to 600 mg/day. Examination by a throat specialist at the sixth week confirmed increased fibrosis in the resolving laryngeal lepromas. The fibrosis aggravated dyspnoea and necessitated the addition of corticosteroids to his treatment. Recently he had a fatal attack of acute respiratory obstruction which appeared to be due to mucoid secretion, not to the medication he was receiving.

DR. GRACE WARREN: All our patients have had liver function tests done regularly every 3 months for 12 months. As all these patients were in reaction, the majority showed definite signs of abnormality at first, particularly inversion of the albumin : globulin ratio, but this tended to revert to a normal pattern. Electrophoresis was carried out on all these patients; in 6 months the electrophoretic patterns had returned to normal in the majority. Results of other tests tended to follow the same pattern.

DR. A. RENDERS (BRUSSELS): The accompanying colour plate (p. 35) shows the remarkable clinical improvement, especially in cutaneous lesions, typical of 4 of the 34 patients treated with G 30 320 at a Leprosarium in the Congo. In one patient with lepromatous leprosy there was considerable reduction in the elevation of the nodules after 18 months' treatment with this product. Another case of borderline leprosy showed a considerable clinical improvement after 18 months' treatment with G 30 320. Another patient who came to the Leprosarium, guaranteed non-treated, who after being treated for 3 months with a dose of 300 mg/day of G 30 320, left the leprosarium without permission. But even in 3 months there was remarkable improvement in this patient. A patient with obvious nodular lepromatous leprosy showed the difference after only 6 months' treatment with G 30 320.

Neurological Aspects

CHAIRMAN: That concludes all the straightforward clinical side apart from neurology, in conjunction with which there are several questions to be answered. In lepromatous leprosy, does sensation improve during treatment with G 30 320? Is there any relation between G 30 320 and nerve pain? How much does the drug help in established neuritis, and can it prevent or in any way affect the development of neuritis in previously untreated patients who receive G 30 320 as their first drug?

DR. KARURU: A part-Chinese, 37-year-old man, was admitted 2 years before receiving the

drug: he had glove-and-stocking anaesthesia, was lepromin positive, and also had lepromatous nodules. He was diagnosed as dimorphous leprosy. After the eleventh month of treatment with G 30 320, he regained sensation in the upper part of the leg. Since I took no biopsy, I was unable to do a proper neurological study, but the fact remains that sensation returned.

PROF. GATT : We had 4 lepromatous patients with severe neuritic pains. Improvement was rapid after the second week of G 30 320 treatment, with disappearance of the pain.

DR. A. KARAT: We have studied changes in sensation over a period of 6 months, carefully mapping the areas in the upper and lower limbs every month. To date, in the 24 patients under observation, we find no change whatever in sensory modalities as compared with the beginning of the trial.

CHAIRMAN: How does this compare, say, with patients treated with dapsone?

DR. A. KARAT: The same.

DR. W. JOPLING (LONDON): Swelling and pain in peripheral nerves may be part of a lepra reaction in lepromatous leprosy, and is one of the aspects of the reaction which will respond to treatment with G 30 320. The important thing here, as in the management of other aspects of lepra reaction, is the dosage used. With a small dose such as 100 mg every other day, there might actually be a recrudescence of neuritis, but by increasing the dose according to need, the neuritis and other aspects of lepra reaction can be brought under control. I think this question of dosage according to patients' needs is one that must be considered very seriously.

DR. S. G. BROWNE: In early lepromatous disease, G 30 320 is valuable because it hastens clinical and bacteriological cure. In other words, the patient is cured before he gets to the stage of reversible or irreversible polyneuritis. There is, however, no evidence that G 30 320 is superior to dapsone or other anti-leprosy drugs in this respect. In early established neuritis with inflammation and oedema, the general clinical picture of acute exacerbation will respond to G 30 320 and the polyneuritis will improve, with concurrent improvement in the sensory and the motor modalities. That would be similarly reversible by other antileprosy drugs if they had a similar antiinflammatory action. In established, fibrotic polyneuritis there is little or no response. The most dramatic response is, of course, in acute inflammation with localized swelling and tenderness of the peripheral nerves at sites of predilection. As I reported some years ago, in these patients there is a substantial and rapid improvement in the pain and tenderness in the nerve trunks.

DR. B. LEIKER (HOLLAND): In Holland, 5 borderline tuberculoid cases with marked nerve involvement, pain and swelling have been treated with G 30 320, 2 patients with 100 mg daily, one patient with 300 mg twice a week, and 2 patients with 100 mg every second day. All showed active, some reactive, skin lesions and I regard the administration of sulphones in these cases as most risky. I should prefer to start with steroids before giving sulphones. These 5 patients were treated with G 30 320, 2 of them initially receiving a moderate dosage of steroids. None has shown an exacerbation; pain and swelling subsided, in all, in 3 within 4 months, in one within 5 months and in the fifth patient within 6 months. The steroids given to 2 patients could be withdrawn after a few months.

DR. R. C. HASTINGS: Every 6 months we usually do motor conduction velocities, with more frequent sensory examination and manual testing of motor power. In brief, we have seen no detectable trend in over 3 years' experience with G 30 320 although these parameters vary somewhat.

DR. F. IMKAMP: We found that in neuritis which was part of the ENL (erythema nodosum leprosum) pattern, the pain and also the swelling of the nerves responded to an increased dose of G 30 320 according to the individual needs of the patients. I cannot say anything about changes in sensitivity, as we were dealing with longstanding lepromatous cases which had been suffering from erythema nodosum for many years.

DR. GRACE WARREN: I should like to agree with what Dr. Jopling said about the neuritis being part of the lepra reaction. In our cases we found that this was so. Regulation of the dose of G 30 320 would control lepra reaction, and it also controlled the neuritis. One particular patient (No. 1685) required 200 mg/day to control his reaction and neuritis, and after he had had no neuritis for 6 to 8 weeks complained one morning of neuritis. After careful questioning, which took 24 hours to extract the truth, he owned up that he had 12 capsules of G 30 320 in his locker which he had not taken. He went back on his full dose, was neuritis-free a fortnight later, and has stayed free. Whether it is coincidence or not I leave to the imagination, but it is the only recurrence of neuritis we have had in patients on G 30 320.

CHAIRMAN: Thank you, Dr. Warren. This brings up a very important point, which is that in all scientific work in leprosy you cannot completely trust the patient. It reminds me of that very honest and interesting paper, which was briefly reported in *Leprosy in India*, of a trial of Ayurvedic medicine in lepromatous leprosy. In this, about one-third of the patients improved, but it was found that those who improved had sulphone in the urine. I admire the author who published that account—it was a lesson to us all.

DR. A. KARAT: In the reaction group our findings are entirely in agreement with Dr. Jopling's. The results with 300 mg of G 30 320 daily are infinitely superior to those with 15 mg of prednisolone in the Grade 3 and 4-plus reactions. I am referring only to the acute painful neuritis that occurs concurrently with erythema nodosum. While conduction velocities, muscle function and sensation remain unchanged in both groups, the relief of pain was gratifying and significant.

DR. E. J. SCHULZ: We have treated 13 patients with neuritis, 8 of them were part of our ENL group and 5 with neuritis alone. All improved and most cases were completely controlled. Some required up to 300 mg daily. Two relapsed after treatment was stopped.

2. G 30 320 IN TUBERCULOID AND BORDERLINE LEPROSY

CHAIRMAN: We shall move on to the value of G. 30 320 in tuberculoid, borderline and indeterminate leprosy. A number of speakers have already slipped in a few words about this.

DR. R. E. PFALZGRAFF (NIGERIA): For about 5 years I have been using steroids much more freely than most people recommend, primarily in patients with tuberculoid or dimorphous (near tuberculoid) leprosy. Steroids are most valuable in these patients. However, with G 30 320 we can begin to consider omitting steroids in such cases.

In one patient under treatment with dapsone, there were signs of slight reaction in his skin lesions, but more significantly he had large and painful nerves. In similar patients, I would have used steroids, but I decided to try 100 mg/day of G 30 320 and the result has been good, without steroids. The ulnar nerve in this patients was roughly 12 mm in diameter by caliper measurement, and quite painful. About 4 months later, the diameter was about 9 mm.

What has been said about lepromatous patients is completely true of tuberculoid patients, of whom we see many more. It looks as if G 30 320 will make a great difference in the treatment of the problem tuberculoid case.

PROF. J. GATTI: We had 3 tuberculoid patients free of skin lesions but with residual neuritis who were treated with 300 mg/day; there was an improvement after the second week of treatment, with disappearance of the ulnar pains and subjective sensations.

3. G 30 320 IN SULPHONE-RESISTANT LEPROSY

CHAIRMAN: We will move on to the value of G 30 320 in patients with sulphone resistant leprosy. This is a subject that has largely developed since the last international conference and, in particular, with the use of the Shepard foot-pad technique, giving laboratory proof of sulphone resistance that has been suspected clinically. A number of papers have been published on this subject and Dr. Tolentino has already told us about one patient with presumed sulphone resistance who responded very well indeed to G 30 320. I saw him just a few weeks after he started the drug, and was very happy with his progress even at that early stage.

DR. J. M. H. PEARSON: We have a series of between 20 and 30 patients with proved sulphone resistance and I have already shown the response in terms of fall in morphological index. Sulphone-resistant patients respond in just the same way as previously untreated patients. Clinically, over periods of up to 4 years, improvement has continued on gradually reducing doses of G 30 320. We have had no cases of G 30 320 resistance so far. Three patients treated for just over 4 years with G 30 320 have all responded satisfactorily. One who was strongly lepromatous has now become smear-negative in the skin. The others have been treated for periods of a few months to about 3 years.

DR. R. C. HASTINGS: We have only one patient with foot-pad proven sulphone resistance who has been on G 30 320 for about a year; he has responded quite well.

DR. S. G. BROWNE: We have 2 cases of foot-pad proven dapsone resistance, and 3 suspected cases. All—even those whose condition was complicated by severe exacerbation—have responded very satisfactorily to G 30 320 up to a period of 29 months, and no case of G 30 320 resistance has developed.

DR. D. LEIKER: We have no cases of proven drug resistance, but I regard cases that have been treated for 10 years with sulphones and have not improved bacteriologically in the last 3 to 4 years as most likely to be resistant. These, and patients with signs of exacerbation (or increases in the bacillary index, and in the number of intact bacilli) have responded very well to 100 mg of G 30 320/day. Altogether, we have 14 patients now on treatment who have received G 30 320 for between $1\frac{1}{2}$ and $2\frac{1}{2}$ years. There is so far no evidence in the smears or the biopsies of resistance to G 30 320.

CHAIRMAN: The small numbers of lepromatous patients who relapse after 10 years or more of treatment, and develop active lepromatous leprosy again after, in some cases, going almost smear-negative, are becoming increasingly important. A number of workers, some of whom have spoken briefly just now, have written on this subject, and in particular they have recorded the value of G 30 320 in sulphone resistant patients. I have felt it my duty as Chairman to remain as impassive and as unenthusiastic as possible, but this is one subject on which I cannot hide my enthusiasm. These patients are cropping up increasingly. As I have travelled round different leprosaria, I have always been shown a few of them, and I think we will be finding them more and more over the next few years. As clinicians we must particularly look out for them.

DR. E. KARURU: One patient of particular interest to me was a Fijian male, aged 57 years, who was first admitted to Makongai in 1941 with lepromatous leprosy, and treated with chaulmoogra for 8 years with no change except that he started to develop dermatitis at the end of that period. When dapsone was introduced in 1949, he was considered suitable for trial. He developed skin reaction as soon as he was started on the drug. Several months later, he was again given sulphone, but the skin reaction was more severe and accompanied by marked oedema, so the treatment was stopped. He was then put on chaulmoogra for another year before starting him on amithiozone, which caused no

ill-effects, and resulted in recovery 8 years later. He was discharged in 1958, but for some reason did not continue taking his tablets. He relapsed in 1963 and he was re-admitted to the hospital. On re-admission he showed lesions of the 2 polar types of leprosy and was classed as dimorphous. Thiacetazone was given again in larger doses than originally, but his condition became progressively worse. After 8 months it was evident that another drug had to be used. Thiambutosine was tried, but 6 months later he suffered nodular reactions and developed a right foot drop. The drug was discontinued, and prednisolone given to control the reaction. Amithiozone was tried again in small doses of 50 mg, slowly increasing to 100 mg/day. Five months later he developed dermatitis. The patient was found to be allergic to several drugs, even including the usual preparation of procaine. Before G 30 320 was tried, his B.I. was worse than before (deteriorating from 0 to 3.5), and the clinical condition was even more severe. After 2 months' treatment with G 30 320, his lesions were clearly receding, the nodules were flattening, and it became clear that this was the drug that we had been seeking. As one of the members of the staff said, "Thank God the drug is doing something for this poor fellow."

CHAIRMAN: Another problem is the patient resistant to one drug who cannot take sulphones because of sulphone allergy. Drs. Pettit, Pearson and I have been studying a small number of patients with thiambutosine resistance, who also had sulphone allergy and could not take dapsone. In these patients, too, we found a perfectly normal response to G 30 320. If no one else has any contribution about the value of G 30 320 in sulphone resistance, let us proceed to the problem of lepra reaction.

4. REACTION-NEW CASES

CHAIRMAN: One panel on reaction—which was, I think, at the Madrid Congress—talked about lepra-reaction and erythema nodosum leprosum. The panel on reaction at the last Rio Congress spoke about leprosy-exacerbation, which was the old lepra-reaction, and about lepra-reaction, which was the old erythema nodosum! As Dharmendra subsequently wrote: "They made confusion worse confounded". If you are speaking of reactions in lepromatous leprosy, which produce erythema nodosum leprosum (ENL) skin-lesions, may I suggest it might be helpful if you call them "erythema nodosum leprosum", no matter what the last panel said. Then we shall at least know that you mean the reaction that occurs in lepromatous leprosy, giving ENL skin-lesions often accompanied by neuritis, iritis, orchitis and arthritis as well. If you are talking about reaction in non-lepromatous patients, please make that quite plain too.

I suggest that we take lepra-reaction in 2 stages: first, in previously untreated patients, especially lepromatous cases—what is the incidence of reaction to ENL, whatever you like to call it, during a standard course of antileprosy treatment? Second, what is the effect of treatment with G 30 320 compared with steroids, potassium antimony tartrate, aspirin, chloroquine, etc., on established reaction?

How much ENL do we see in new, previously untreated patients, undergoing their first course of treatment? Dr. Stanley Browne was the first person to comment on the possible antiinflammatory action of G 30 320 in his original series of patients, and I should like him to start the ball rolling.

DR. S. G. BROWNE: I shall attempt to abide by the Chairman's definition of "reaction". I shall sometimes use the word "reaction" and sometimes "ENL". Leprologists of long experience have seen acute reaction in *untreated* patients with lepromatous leprosy.

In our early observations (I include my friend and colleague, Dr. Hogerzeil, who was my co-worker), we observed that 2 patients with lepromatous leprosy developed acute reaction during the first 3 weeks of G 30 320 treatment. After that, no patient in the series developed acute reaction. This suggested to us the possibility that G 30 320 might have some action in suppressing the development of acute reaction in lepromatous leprosy. No claims were made at this stage, because this could easily have been a self-limiting, transient phenomenon which, as we all know, occurs not infrequently in lepromatous leprosy.

In subsequent series of patients under

G 30 320 treatment for lepromatous leprosy, I have personally observed only one patient who has developed acute reaction during adequate therapy with G 30 320—adequate in the sense of producing clinical and bacteriological amelioration. This occurred after 3 months of treatment and responded to doubling the dose from 100 to 200 mg/day. These early observations naturally required rigorous examination not only in Africa, where acute exacerbation in lepromatous leprosy is both less frequent and less severe than amongst the less deeply pigmented peoples, but also in India, and further East—Korea, the Philippines, Malaysia, etc.

That, Mr. Chairman, is as far as I would go with the role of G 30 320 in preventing lepra reaction developing in patients who, to the extent of one-half to two-thirds, might be considered prone to develop such reaction during the initial course of treatment of leprosy.

DR. W. JOPLING: One can forecast the patient who is likely to develop ENL reaction from the commencement of treatment by a study of his B.I. and M.I. If nearly all a patient's bacilli are in a solid-staining form, about 6 months will elapse before he develops ENL. The majority of my patients, of course, do develop ENL the majority of patients or those who develop ENL are light-skinned. On the other hand, if a patient has a preponderance of fragmented and granular bacilli at the time we first see him, treatment may precipitate ENL reaction within a matter of a few weeks. I think this is the important thing to get clear in the first place.

DR. D. LEIKER: We have given G 30 320 to 9 previously untreated patients, who had not shown reactions (ENL) in the 2 years prior to G 30 320 treatment. Eight did not show any reactions during periods of G 30 320 treatment ranging from 11 to 30 months; one patient showed a single reaction. On the other hand, among 16 lepromatous patients with complications prior to G 30 320 treatment, 12 have shown one or more ENL reactions while receiving the drug.

In none of the patients was evidence found that the reactions were provoked by or became worse during G 30 320 therapy. In 9 patients,


Colour Plate. The response to treatment with Lampien (see text).

reactions did not recur after the first few months of treatment. In one patient the reaction stopped after 3 months, but recurred in mild form after 8 months of treatment; 3 months later, it stopped again, and has not recurred. In 2 patients G 30 320 did not seem to make any difference. The reactions became worse and we had to give high doses of steroids. In one of them the dosage of G 30 320 was increased to 300 mg/day and that again did not make the slightest difference-the 2 patients died. Unfortunately, this happened right at the beginning of the trial which worried me very much. Autopsy was performed and we found no evidence that death had anything to do with G 30 320. In one case the cause was quite obvious-a perforating ulcer due to prolonged high dosages of steroids. In the other case the cause of death was not discovered, but G 30 320 was probably not the cause; no evidence in the liver, spleen or other internal organs suggested that it had anything to do with the drug.

CHAIRMAN: The second patient, cause of death unknown, was he in severe ENL reaction at the time of death?

DR. D. LEIKER: He had continuous reactions and each time we had to increase the dosage of steroids. As soon as the reaction subsided, we tried to reduce it gradually again from dangerously high levels. Immediately severe reaction developed, and we had to raise the dosage again, and this happened 10 or 15 times within 7 or 8 months. Gradually the general condition deteriorated and the patient died. There was an abscess from which salmonellae were cultured. This may have had something to do with the death.

CHAIRMAN: You said you increased the dose of G 30 320 in one patient to 300 mg a day. What was your standard dose?

DR. D. LEIKER: 100 mg/day in all cases.

DR. M. H. PEARSON: Our experience with G 30 320 in patients previously either untreated or resistant to other drugs—and in effect untreated—before G 30 320 was given is consolidated in Table 1. The columns labelled "ENL, 1 2 3 4" represent degrees of severity of ENL. Roughly, Grade 4 means a reaction

TABLE 1 Incidence of ENL during treatment with G 30 320

Dose of	Period	No. of	No.	of cas develo	es of 1 oping	ENL 1		
G 30 320	(months)	cases	1	2	3	4		
100 mg t.d.s.	0-6	16	1	-	_	-		
_	6 - 12	4	-	-	1			
100 mg daily	0-6	5	24	1	-	-		
	6 - 12	8	1000	1	1	1		
	12 - 18	6	-	1		-		
	18 - 24	5		-	1.000	-		
	24 - 30	3	-	-	344			
100 mg 2 or 3	$0 - 4\frac{1}{2}$	9	-	-	-	-		
times weekly	$4\frac{1}{2} - 1\frac{1}{2}$	3	1		-	-		
•	12 - 18	3	12	100	_			
	18 - 30	2		100	-			
	30 - 36	3	-	-	1.000	-		

needing large doses of steroids, and Grade 3 small doses, while Grade 2 patients can just be managed without steroids, and those in Grade 1 have a very mild reaction. The top 2 sections show the incidence of ENL in patients treated with 100 mg of G 30 320 3 times a day. I should emphasize that these were all pure lepromatous patients at biopsy; no borderlinelepromatous (BL) cases were included in Table 1. In one of 16 cases treated for 6 months minimal ENL developed in the first week or 2 of treatment and then subsided. Four continued on G 30 320 3 times a day for another 6 months.

During that period one patient developed moderately severe ENL, which was transient but needed steroids for a short period. He had had very severe ENL previously and was sulphone-resistant.

Among the patients given 100 mg of G 30 320 daily, 5 were treated for 6 months, one developing mild ENL of Grade 2. Eight were treated for 6 to 12 months, some having previously received 300 mg daily; others continued on 100 mg daily from the initial treatment. Three of these developed ENL, 2 fairly seriously and one moderate. Of 6 patients who continued treatment for 12 to 18 months, one developed ENL mildly, while no reaction was seen among the 8 patients treated for between 18 and 30 months with 100 mg daily. In a series of 9

TABLE 2 Incidence of ENL during treatment with dapsone

Group	Ear (0-6 mo	ly nths) (Lat (6-12m)	te onths)
1	1-2	3-4	l-2	3-4
Lepromatous leprosy (LL) treated with dapsone 50 mg twice weekly	4/16	0/16	6/14	2/14
Lepromatous leprosy (LL) treated with dapsone 300 mg twice weekly	10/76	3/76	23/70	14/70

patients treated with 100 mg twice weekly for $4\frac{1}{2}$ months, there was no ENL, while one of 3 patients who continued to 12 months developed a minimal reaction. The final groups, 12 to 36 months, represents a different group of patients previously treated with larger doses of G 30 320. None developed ENL.

For comparison, Table 2 shows the incidence of ENL in patients treated with DDS in 2 other

CHAIRMAN: Next, we should like to discuss the value of G 30 320 in patients with established reaction. This is a subject that has aroused some controversy in the leprosy press.

DR. JOSE BARBA-RUBIO: Knowing that the reaction in some cases can disappear without any treatment and, in others, does not disappear in spite of everything that is done, we made a selection of patients with very severe reactions.

The 10 patients chosen suffered from continuous and prolonged lepra reactions and, with only one exception, they had had to suspend every treatment that was tried. The initial dosage of G 30 320 was 300 mg daily, reduced to 100 mg once the reaction was controlled.

The results were very good in 3 cases, good in 4, fair in 1, and bad in 2. Of the 10 patients, 7 are now under treatment with dapsone in doses of 100 mg daily, and one is having thiambutosine. In one case with neuritis before treatment with G 30 320, the neuritis continued and increased. Generally, I believe that G 30 320

trials (not carried out simultaneously). Among those given 50 mg twice weekly, 4 out of 16 developed moderate ENL in the first 6 months, and a total of 8 (moderate and severe) in the second 6 months. These figures are similar to those from a previous study (lower half of table) using 300 mg of dapsone twice a week. Comparison with the results in G 30 320-treated patients suggests a lower incidence of ENL with G 30 320 than with standard dapsone therapy.

CHAIRMAN: Thank you, Dr. Pearson. We have now discussed the incidence of ENL in new patients getting G 30 320 as their first drug and Dr. Pearson's figures compare it with the incidence experienced with dapsone in the same leprosarium. However, I think it is only fair to point out that this was not under controlled conditions. The patients were not admitted and allocated by random selection to one group or another. Once again, one would like to have an absolutely controlled trial, but I am personally quite impressed with those figures.

5. ESTABLISHED REACTION

is a good drug in those cases where other drugs fail to control lepra reaction.

DR. S. G. BROWNE: The original observations on the curative role of G 30 320 in established acute reaction showed that the drug appeared to be effective in 10 patients with severe Grade 4 or 3 reaction of long duration (16 to 36 months, with an average of 24 months). The duration of treatment in these patients before reaction began had been as follows: 5 patients, 5 to 9 months; 2 patients, 10 to 19 months; 3 patients, over 20 months. They were all severely ill and corticosteroid dependent. On many occasions, other anti-inflammatory drugs had been prescribed, but to no effect. Repeated attempts at weaning from corticosteroid dependence had been made without success. Invariably reaction was precipitated by a slight reduction in steroid dosage. When these patients with established severe reaction started G 30 320 treatment, they were steroid dependent to the tune of 10 to 15 mg prednisolone daily. Even when controlled on this dose, 10 mg of dapsone was sufficient to precipitate acute exacerbation.

This trial, and other similar trials with which I have been associated, used the patients as their own controls, to determine the lowest maintenance dose of corticosteroid that could be given. G 30 320 was then introduced, beginning with 100 mg/day, and the steroid dosage gradually reduced. If reaction reappeared, then the dose of G 30 320 was increased. It was found that all patients could be weaned from corticosteroid dependence, by giving G 30 320 alone. The maintenance dose of G 30 320, which depended on the circumstances, was 100, 200 or even 300 mg/day, the higher dosage being gradually reduced until, in some cases, reaction reappeared. The quantity was then increased again in order to control the reaction completely. In all patients it was possible permanently to control the reaction and then gradually to increase dapsone as a therapeutic agent.

CHAIRMAN: Dr. Browne emphasizes the importance of some sort of control, and the method of using the patient as his own control is one of the possible ways of doing a controlled trial in erythema nodosum leprosum or lepra reaction—whichever name you prefer. Next, I would like to call on Dr. Hastings, who has recently published a paper on G 30 320 and ENL.

DR. HASTINGS: Briefly, we attempted to match 6 pairs of patients with chronic ENL, requiring corticosteroid therapy. They were divided into 2 groups and we attempted to match, as accurately as possible, age, sex, severity of ENL and so forth. Generally they had pure lepromatous leprosy with erythema nodosum. We measured the steroid requirement to prevent significant neuritis and ulcerating eyrthema nodosum, and, in the course of some 6 months, we felt that the G 30 320 group, which averaged 216 mg/day, did better than a comparable group treated with solapsone. I might add that each dose of the G 30 320 was swallowed in the presence of nurses on duty, and the solapsone was, of course, injected, so we felt that all patients were indeed taking the drug in full measure.

DR. IMKAMP: I can only confirm the findings of Dr. Browne. Our trial consisted of 18 severely corticosteroid ill. dependent lepromatous patients, who, after an average of 2 years and 7 months of steroid treatment, were started on 100 mg G 30 320 daily, except in one case, who started with 200 mg daily. All were eventually weaned off prednisolone; the dose of G 30 320 was increased according to individual needs, no patient getting more than 400 mg/day. Out of 8 female patients, 7 have been changed to dapsone after an average of 22 months on G 30 320, and 14.4 months after the ENL was controlled. Of the 10 male patients, 7 were changed to dapsone after an average of 22.2 months on G 30 320, and 14.4 months after the ENL was controlled. Of the 10 male patients, 7 were changed to dapsone after an average of 22.2 months on G 30 320, and 14.4 months after the ENL was controlled. All those patients improved in health, and were eventually discharged from hospital; several are already discharged from the leprosarium.

One patient with pure lepromatous leprosy, sent to us by another doctor because she could not be treated with any leprosy drugs, had continuous ENL and could be controlled only with 5 mg of prednisolone twice daily. When she arrived she was in fairly good condition, the ENL was controlled, the B.I. 5, and the M.I. 0%. We gradually decreased the prednisolone without giving any anti-leprosy drugs, and ENL developed when she was having 5 mg prednisolone. We gave her first a course of stibophen, but she did not respond, and then we gave her 100 mg G 30 320 daily. About 10 days later she walked, and starting eating. Her temperature was normal and gradually she became stronger; her ENL was completely controlled on 100 mg daily. Then we ran out of 1 mg tablets of prednisolone and made up a suspension, gradually reducing the dosage by 1 mg a month. Then in July, when she was on 2 mg and reduced to 1 mg, she had another bout of ENL. We were then told that the suspension was probably not stable, and she may have been receiving much less than we expected. She developed larvngeal oedema and G 30 320 was

increased to 400 mg but prednisolone remained at 1 mg daily, and she was treated with oxygen. She recovered completely. We now had taken off 0.25 mg of prednisolone; 2 days later she had a slight temperature of 99° (37.2) and a swollen lip which responded to an increase of G 30 320 from 300 to 400 mg. She has done very well, and we intend to decrease her prednisolone by 0.25 mg every month.

DR. W. JOPLING: My experience with G 30 320 has been in the management of lepromatous cases with ENL reactions, and there are 2 groups that I should like to report briefly upon. In the first instance, about 5 years ago I tried with a small group of 5 patients giving very small doses of G 30 320, 25 or 50 mg twice a week. Over several months of observation, I found no improvement whatsoever in ENL reactions. The second group consists of 24 patients all with severe ENL reactions, 8 of whom had to be controlled by steroids. In all these 24, a minimum of 100 mg G 30 320/day and a maximum of 400 mg/day completely controlled the erythema nodosum reactions. The importance of increasing dosage with need was brought home to me with a patient from Liverpool, who was on TB 1 (thiacetazone) treatment because he is sulphone resistant. He developed erythema necroticansa necrotic, bullous, form of ENL-and I let him return to Liverpool. (Most of my patients are out-patients; they have no ENL in hospital, but when I send them out to work, down they go with ENL, because by that time there is sufficient granularity of their bacilli.) He phoned from Liverpool to say: "I have taken G 30 320 for a month, 100 mg a day, my erythema necroticans is no better; I am in a pitiful condition, covered with sores." I replied: "Don't come to London, increase the dose of G 30 320 to 300 mg a day", and I had a letter 2 or 3 days later saying: "Wonderful, entirely under control".

CHAIRMAN: Thank you, Dr. Jopling, I am very interested to hear of your further experiences. The speakers so far have all been in favour of G 30 320 in controlling reactions, although Dr. Jopling has pointed out the importance of dose. Dr. Pettit published a carefully designed trial about 2 years ago, which was not favourable.

DR. PETTIT: I am the one that caused all the trouble. If I can introduce myself, I started as a dermatologist, and I am doing mainly dermatology now. I have seen many diseases, as all dermatologists have, which are fluctuant in their course. This makes it very difficult, not only to design clinical trials, but also to make any assumptions on cases that get better 3 days after treatment has been changed.

Maybe people have a little more optimism than I have, and have been anxious to see some patients improve and have not always waited for the full effect of long-term treatment. Dr. Barba-Rubio for instance, in his series of cases had 3 very good successes and 2 almost total failures. You might assume several things from that. Dr. Browne's cases, which were corticosteroid dependent at a dosage of 10 to 15 mg of prednisolone a day, are not what I would have called very bad cases when I was writing this paper. Dr. Imkamp's case that could be ameliorated to some extent by 1 mg a day, I would not have called a severe case of erythema nodosum leprosum. [Dr. Imkamp comments: As a measure of precaution, the dose of prednisolone was reduced by this amount.]

In other words, perhaps the cases that I was working on were more severe than the average. It has already been pointed out that in the East, among the Chinese and the paler-skinned patients, reactions are more severe as well as more frequent. So may be our bases of comparison were not comparable from one country to another. In carrying out a trial of any drug, surely one must maintain the dosage. It is no good playing a game of roulette; the way to win at roulette is to double up. But it is not scientific to say: "If you do not get a response with 100 mg give 200, and if 200 does not work, give 400". As the years go by, you are bound to get a success now and then. It seems to me that if you are going to do a trial you must decide to give such a dose for such a type of disease. The trial I did was an attempt to see whether

100 mg/day works on very severe cases of ENL. Really it was not terribly convincing. If 300 mg/day works in less severe cases I have no experience. I would suggest that the subject is not totally closed.

CHAIRMAN: Dr. Pettit has brought up 2 or 3 points. First, the importance of careful methodology in the design of these trials. Second, the one I mentioned, the importance of dose, and thirdly, the need to take into account the different regions and different races when interpreting results.

DR. E. J. SCHULZ: I hope my trial will be approved by Dr. Pettit. It consists of 2 sections. The first is a comparison of ENL patients before and after the use of G 30 320. There were 28 patients, all having prednisone for varying periods, with an average of 17 months at a dose of 5 to 40 mg daily, even 50 mg in one or 2 cases. At the start of the trial, we gave all patients 100 mg G 30 320 daily. This was increased to 200 mg after 2 weeks, then 300 mg. Later, as we found larger doses to be necessary, some patients were given an initial dose of 200 mg. In 5 cases, it was necessary to increase the dosage to 400 mg daily. The aim of this trial was to control ENL, stop prednisone and continue dapsone (which is given at our institution in a dose of 300 mg a week). The prednisone was stopped in 68% of these patients after 5 months on average, decreased in the others, and all patients improved. Very important was the fact that it took about 5 months for the patients to reach their maximal response; in one or 2 cases the ENL became a little worse shortly after G 30 320 was started. 400 mg daily was necessary in 5 patients, 300 mg in 20, 200 mg in 2, and 100 mg was sufficient in only one patient. None failed to respond.

The second trial contained 2 groups, treatment and control. The first consisted of 16 patients receiving dapsone 300 mg weekly plus G 30 320, 100 mg daily. The second group consisted of 15 patients receiving 300 mg dapsone weekly. All patients had pure lepromatous leprosy and the trial was conducted over a period of 18 months. At the start of treatment, there were 6 ENL patients in each group. After 18 months, there were 11 ENL patients in the group treated with dapsone only; in other words the number of reactions almost doubled. In the group receiving G. 30 320 as well as dapsone, the number of reactors fell by half, from 6 to 3.

CHAIRMAN: Once again the question of dosage crops up. I believe, Dr. Pettit, you used a standard dose of 100 mg daily, 6 days a week.

DR. J. PETTIT: Steadily, regularly, 6 days a week.

CHAIRMAN: This has to be borne in mind in comparing your results with the others we have been listening to.

DR. GRACE WARREN: I have presented some of our findings in the treatment of reaction in a paper, a summary of which is printed on page 60 in the book of abstracts. The trial was designed after the style of Dr. Browne's, using the patient as his own control.

The 30 patients had all been in hospital with chronic erythema nodosum leprosum for a minimum of 2 years, some of them for 4, 5 and 6 years; and 4 of them were on prednisolone. I will not say they were prednisolone dependent, because only one of them was on a fairly high dosage. We aimed at finding out the dose of G 30 320 required by these patients, and the majority commenced at 300 mg/week. This was increased every 4 to 6 weeks until the reaction was controlled. Three patients required only 300 mg/week, 13 patients required 600 mg, 9 patients required 900 mg, and 4 patients required 1200 mg/week. Once all reaction had been controlled for a minimum of 6 weeks, we attempted to reduce the dose of G 30 320, and this is where we began getting some very interesting findings.

In some patients who initially required 900 mg, we were able to reduce to 400 mg a week, whereas some patients could not tolerate any reduction. They would go back into erythema nodosum leprosum—though not immediately, and I have not seen an increase of G 30 320 control reaction within a few days either. Maybe I have not increased it enough. Increased dosage usually takes a fortnight at least to make much difference in reaction. Because this is a fluctuating complaint, we did not alter our dosage more often than once every 4 or 6 weeks; so that we had enough time to see whether spontaneous alteration would take place. I mentioned earlier the boy with neuritis who relapsed, and we have had one or two other cases who appeared stable on low dosage and then suddenly went into a reaction again, but in no case were these reactions as severe as they had been before the patient was on G 30 320.

I was interested in the comments we had earlier on the cases which failed to respond. We had one patient (No. 1333) on 20 mg prednisolone for 12 months who, 8 weeks after commencement of G 30 320, went into an extremely severe ulcerating type of reaction. We did not stop the G 30 320 or change the dose of prednisolone. Eventually she came out of reaction and after 6 months she was completely off prednisolone, and is now on 1200 mg of G 30 320 weekly with good fall in the B.I. She gets an occasional mild ENL—one or 2 spots at a time-of purely nuisance value. Her general. condition is now so much improved that she has requested discharge after over 18 months in hospital.

DR. K. MAHMUD (DJAKARTA): My trial with G 30 320 was started 3 months ago, so this is only a progress report, but nevertheless it confirms the other trials reported. As you know, in Indonesia, we also have trouble, especially with patients developing reactions on sulphone. We first tried G 30 320 in 13 patients, all admitted to the leprosarium, 7 of them previously controlled by corticosteroid or other anti-reaction drugs. We started G 30 320 at 100 mg/day for 6 days, and then increased dosage to 200, 300 mg and so on to control reactions. After 3 months, 4 of the 13 patients had no reaction at all, with improving general condition and falling erythrocyte sedimentation rate. They feel quite happy that they are free from the burden of suffering after many years. The other 9 patients had reactions, controlled in 5 by G 30 320, 200 mg/day, in 2 by 300 mg/day, and in one by 400 mg/day. In the final case we increased the dosage to 600 mg/day, but still

could not control the reaction without 15 mg of prednisolone daily. But now we are decreasing the steroid dosage, and I think we shall have the same experience as our colleagues here. Of the patients who developed reactions, 4 only had one and up to now there is no further reaction; 4 developed reactions for a second time after 3 or 4 weeks, but the second was milder and shorter in duration.

One of the patients, who was really sick when admitted to the leprosarium, improved remarkably after only one month. Before starting G 30 320 he could not walk and was bedridden. After 3 months his weight increased by 10%, and he could walk.

DR. KARAT: Concerning methodology, I should like to point out that the very faults which Dr. Pettit pointed out in the other trials apply to his own, namely, that there were 2 variables; first the subjective interpretation of severity of reaction to determine steroid treatment. And second, as I interpret his paper, the steroid dose given went up and down, depending on the clinical status of the patient. I do not see how adjustment of the G 30 320 dose differs in principle from adjustment of steroid dosage.

Briefly, 23 cases were under trial in my group, of which 4 were not on a controlled trial; 2 of them needed 30 mg of prednisolone/day, one needed 45 mg/day, and another 60 mg/day, for periods ranging from 18 months to 2 years. All of them came to me with hypertension and Cushingoid facies, still having almost continuous episodes of necrotizing erythema nodosum with haemoglobin ranging from 6 to 8 g. These people were given 300 mg of G 30 320/day, and the patient needing 60 mg of prednisolone took 12 weeks before he became completely controlled, with no further steroids. In all cases, steroids were withdrawn in between 2 and 4 weeks, using intermittent administration of ACTH. On admission, prednisolone was stopped overnight, and patients received on alternate days injections of long-acting ACTH. In all, steroids were completely withdrawn and the erythema nodosum leprosum (which was 4+if not 5+, in severity in this group) was controlled. Among the 19 control patients, 10

belonged to the prednisolone group, and 9 to the G 30 320 group. In the latter the average duration for control of reaction ranged from 14 to 28 days. No first reactors and no patients below 3+ in severity were admitted into the series. The average number of reactions in these patients was 30 prior to admission to trial. I would consider them severe reactions by any standards, anywhere in the world.

CHAIRMAN: There is obviously a lot to discuss here, and I would like to ask just one or 2 questions before we stop. What I am particularly interested in with regard to lepra reaction and ENL is whether there is an absolute suppressive dose of G 30 320. I have been noting down the doses that contributors have suggested; some patients were controlled by 200 mg, some by 400 mg/day, and one patient was not controlled even by 600 mg/day. So it looks as if there is a variable range. I wonder if anybody is quite sure that he has found an absolute suppressive dose? How about the permanence of the controlled state once the reactions have been brought under control? Have we seen a picture emerging of any special time limit at which it is safe to take patients

off G 30 320 perhaps, and put them back on to dapsone?

DR. F. IMKAMP: Yes. My patients were taken off G 30 320, 14.4 months after their ENL was controlled, and put on a low dosage of dapsone 22 months after the G 30 320 treatment started.

CHAIRMAN: Thank you. This is a point we have to note, and I hope those who are preparing papers will stress it. We have been interested to see how long patients have been kept on G 30 320 before returning to dapsone, and the relapse rate of reactions afterwards or while still on G 30 320.

We are deliberately avoiding all experimental work. Otherwise, I would have asked Dr. Vischer to report on his experimental work on the anti-inflammatory action of G 30 320, but those of you who are staying for the Congress will hear him report it there. However, I was this morning informed that the leprosy research group at the National Institute for Medical Research did find an anti-inflammatory action of G 30 320 in mice, using the carrageenin test, but no immuno-suppressive activity against skin homograft rejection in mice.

6. PIGMENTATION AND TOXIC EFFECTS OF G 30 320

CHAIRMAN: We have not, I am afraid, discussed toxicity and side-effects, or pigmentation. A question I would like to ask—I think Dr. Stanley Browne probably has the answer—is how long does pigmentation persist after stopping G 30 320?

DR. BROWNE: It varies with the initial degree of cutaneous pigmentation, and with the degree of pigmentation produced by G 30 320, which in turn, may or may not depend upon the dose given. I am sorry to be so vague, but all these things are variable. Pigmentation may disappear within 3 months; it can persist up to 18 months, sometimes as diffuse hyperpigmentation, of slatey-grey appearance, either in the lesions themselves, especially when they are thick and fibrotic, or in apparently normal skin. DR. G. WARREN: Three of my patients havs been off G 30 320 for 3 months; so far there ie some obvious noticeable change, but they are still definitely pigmented, though this is fading.

DR. L. HOGERZEIL: When I went back to Holland, I saw leprosy patients such as I had very seldom seen in Biafra in the years I was there. I have tried G 30 320 on 6 patients who had previously been treated for an average of 16 years each. This was almost unknown in Biafra; they were all resistant to thiambutosine and all intolerant of dapsone. They were just drifting on, given steroids intermittently in dosages between 30 and 60 mg. They have now been treated with G 30 320 for $1\frac{1}{2}$ to 2 years. It was 9 months to a year before the first reactions reappeared in much milder form, and after about half a year it was possible to resume very low dosage of sulphone. In the 2 years that we have treated these poor patients in Holland, they have begun to make some progress comparable to that normally seen with dapsone. This was out of the question in the previous 14 to 16 years.

TOXIC EFFECTS

CHAIRMAN: Various authors have described gastro-intestinal upsets on daily doses of 300 mg of G 30 320 and above.

DR. D. LEIKER: We have had 2 patients with mild gastric complaints which did not become more serious on G 30 320. I have had to take one other patient off G 30 320 because he had very serious stomach complaints; he vomited and developed a gastric ulcer. Is this exceptional? We switched him over to DPT and had the same results, again gastric complaints. We switched over to thiosemicarbazone and had the same complaints. This, I would say, is exceptional.

CHAIRMAN: Has anybody reported or seen gastro-intestinal upset in doses under 300 mg a day?

DR. D. LEIKER: This patient was on 100 mg/day.

CHAIRMAN: But this was a patient who was having multiple gastro-intestinal upsets. Dr. Hastings, you had a case?

DR. R. C. HASTINGS: We have seen a number of gastro-intestinal upsets in patients receiving 200 mg daily or less.

DR. GRACE WARREN: Some of our patients were complaining of gastro-intestinal disturbances, but when they took their G 30 320 with their main meal of the day we found that everything settled down. That included a number of patients known to have had gastric ulcers before we started and who had no increase in symptoms, which had been controlled by probanthine before G 30 320 was started.

CHAIRMAN: Has anybody observed any other toxic effects, such as dermatitis or leucopenia or anything?

DR. E. J. SCHULZ: I have seen a few cases of dermatitis, but in none could it be shown that G 30 320 was the cause, because the dermatitis disappeared in spite of continued treatment. The results of examination of a patient who came to post mortem 8 months after he had last taken G 30 320 showed no crystals in the jejunal mucosa. Prof. Simson (who does our pathology) reported that crystals were observed in the cortical tubules in the kidney that were similar, or identical, to those of G 30 320.

PROF. J. GATTI: In 15 patients, we observed after 4 or 5 weeks of treatment that the skin became xerodermic, and in 4 cases frankly icthyosiform. The xerodermia may explain the generalized itchiness that was observed on 2 patients. We did not see alopecia.

DR. W. H. JOPLING: Four out of 24 patients (16%) had a generalized pruritus which improved on reduction of dosage. These patients were having 200 mg or more a day, coming down to 100 mg. In no case was it necessary to cease therapy.

DR. S. G. BROWNE: We had one case of exfoliative dermatitis that may or may not be attributable to G 30 320, but certainly occurred during G 30 320 treatment, 100 mg daily; 2 patients complained of giddiness one hour after taking G 30 320, 100 mg capsule on an empty stomach; there again, I would hesitate to attribute that to G 30 320. On the other hand, I have seen a patient elsewhere who was complaining of a severe gastric upset on 200 mg of G 30 320, but when he saw how greatly improved he was and how his fellow patients were getting better on G 30 320, he had no further trouble.

DR. P. D. FOWLER: We have not had any bone marrow toxicity reported that has been definitely related to the drug. One case has been very recently reported in London of a child taking, I think, 200 mg daily over a period of about 4 or 5 months, whose polymorphonuclear leukocytes went down to rather low levels. The dose was reduced, but treatment was not stopped; in this case the white cells rapidly recovered. It was suggested initially that this might have been a toxic reaction to G 30 320, becaused it was the only drug the child was taking. But in view of the fact that there was a natural recovery while the drug was still continued, this now seems rather unlikely.

7. EFFECTS OF G 30 320 ON PREGNANCY AND LACTATION

CHAIRMAN: I would like to know if anybody has experience of the drug in pregnancy or lactation.

DR. F. M. J. H. IMKAMP: Three patients, after being over a year on G 30 320, were delivered of female babies, all normal. One child unfortunately died because the mother, in spite of a warning to come to the hospital and report she was in labour, had one of her friends deliver her in the leprosarium, and the child had subdural haemorrhage (confirmed at postmortem). Physically all the children were healthy, and skin pigmentation was, I should say, normal, though others thought it slightly darker.

DR. E. J. SCHULZ: We had one patient who took 100 mg of G 30 320 throughout pregnancy and had a normal baby. A patient who took 100 mg from about the first or second month had a premature infant following an antepartum haemorrhage. A post mortem was done on this baby and there was no sign of any teratogenic action. The findings of epidural and other haemorrhages were apparently those usually seen in premature babies who have suffered from anoxia before birth.

DR. S. G. BROWNE: One patient, a nurse with severe lepromatous leprosy, was treated with G 30 320 in Eastern Nigeria. She was delivered successively of 2 children. Both babies were rather more deeply pigmented than they should have been. The other patient, who was lactating when admitted to the very first G 30 320 trial, passed on some of the drug apparently in her milk and the baby became rather more deeply pigmented, after passing through the phase of ruddiness.

DR. H. S. PETTIT: A patient I was treating for

Mycobacterium ulcerans infection with 300 mg of G 30 320 daily, was breast-feeding her baby when the diagnosis was made. Her major complaint was that the milk was a bright pink colour, and the baby certainly turned red. I think we must be aware of this, because if there is going to be renal involvement in adults who take an average dose, there might be danger to the kidneys of a breast-fed baby.

CHAIRMAN: The only relevant patient whom I have personally treated was 6 months pregnant when she started treatment. She was thiambutosine resistant, and had sulphone allergy. I left before I knew the result of the delivery, but she probably had a normal baby, because her treatment was started at 6 months, so there was really no question of teratogenic effect.

So, ladies and gentlemen, I would like to thank you all for your co-operation today. In closing I would like to thank one of the few people whom I have not been able to persuade to speak today, and ask him to say goodnight to us: the discoverer of G 30 320, Dr. Barry. Would you close the symposium, Dr. Barry?

DR. V. C. BARRY (DUBLIN): I am afraid I am hardly qualified to close the symposium, in fact I could not have contributed to it. I enjoyed it very much and I learnt a lot. Strangely enough, I do not know anything about leprosy, but I have read a certain amount about it. I have not discovered, nevertheless, what the difference is between ENL and lepra reaction, but I must say I have enjoyed the proceedings very much. My colleagues and I have been working for 21 years on these compounds. The first lead we got was in 1947, and we have now tried 300 similar compounds. None of them is more active than G 30 320 so far. But we have not given up.

POSTSCRIPT

In the light of the preceding discussions, it would seem appropriate to summarize current knowledge of G 30 320 as a guide to the practical use of this relatively little-known drug in the treatment of leprosy.

TOLERANCE AND CONTRA-INDICATIONS

From answers given to a questionnaire distributed at the symposium, the reports were based on a total of 718 patients. Of these, 533 had lepromatous leprosy, 9 tuberculoid, one indeterminate, and 87 borderline, while 88 had had leprosy of unspecified type. The drug has therefore been used in a considerable number of patients in many countries, and no serious toxic effects have been reported with the possible exception of one case of exfoliative dermatitis. Mild gastro-intestinal upsets, occurring in a few patients, have responded to lowering of the dosage. Drug sensitivity rashes have been rare and have been easily controlled. The report of temporary, microscopic abnormalities in the urine requires confirmation and study at other centres. No serious blood dyscrasias have been reported to date.

In general, no definite contra-indication has as yet been discovered for G 30 320. The drug can probably be used safely for out-patients as well as in-patients, provided that the former are examined regularly both at the beginning and at intervals during the course of treatment. Nevertheless, it is recommended that whenever possible regular blood counts should be carried out together with careful checks of the hepatic and renal functions. The drug should be used with great care in patients with known hepatic or renal impairment. On general grounds, caution is advisable in pregnant women, especially during the period of organogenesis. In the 4 expectant mothers mentioned in the discussion who received G 30 320 during the whole course of their pregnancy, no sign of any teratogenic effect of the drug was observed. Simiarly in experimental rats and rabbits, G 30 320 given in a dose of 5 mg/kg bodyweight, caused no damage to the embryo; however, the absence of evidence of damage in these animals does not necessarily preclude a teratogenic effect in man. Therefore, in treating pregnant women with G 30 320, the unknown risk to the embryo must be balanced against the indications for giving G 30 320, especially the serious nature of the acute reactions of leprosy that occur during pregnancy. Thus, in erythema nodosum leprosum, the value of giving this anti-inflammatory, anti-bacterial drug must be weighed against the increased risk of abortion or of still-birth in uncontrolled, or steroidcontrolled reaction, together with the nearcertainty of severe exacerbation of the reaction at the end of the first week of the puerperium. Further experience with G 30 320 in pregnancy is necessary before its use can be fully evaluated or generally recommended for women in the child-bearing period.

The principal disadvantage of G 30 320 remains the drug-induced pigmentation which occurs in most patients. This pigmentation is less acceptable in some races and parts of the world than in others, and patient acceptability must be weighed against the indications for administering the drug. Further research is required on the nature and mechanism of this pigmentation and its reversibility.

GENERAL ASSESSMENT OF G 30 320

Although its mode of action against Myco-bacterium le prae is not yet known, G 30 320 has a definite anti-leprotic effect as measured both in clinical patients and experimentally in the mouse foot-pad infection. Its anti-leprosy activity is of the same order as DDS, although precise evaluation has not yet been carried out, as the results of controlled clinical trials are still awaited. Patients have been treated continuously with the drug for up to $4\frac{3}{4}$ years, and no evidence of drug resistance has been reported. It has been used successfully in the treatment of patients with proven sulphone-resistant leprosy.

There is some evidence that in previously

untreated lepromatous patients receiving G 30 320 as their first anti-leprosy drug, the incidence of erythema nodosum leprosum is less than in similar patients treated with DDS; controlled clinical trials are indicated. In established reaction, the great majority of authors consider that the drug has a very definite anti-inflammatory and reaction-suppressive activity. This is supported by the finding of anti-inflammatory activity in experimental animals as measured by the cotton pellet and the carrageenin tests. However, it has no immuno-suppressive activity, as measured by the classical homograft-rejection test.

INDICATIONS

In patients with lepromatous leprosy infected with sulphone-resistant strains of Myco. leprae, G 30 320 may be considered the drug of choice; it is fully effective in such patients; proven drug-resistance to G 30 320 has not yet been reported; and, since it is given orally, it is easy to administer. It is the drug of choice in patients suffering from thiambutosine-resistant leprosy who also have allergy to the sulphones. It is indicated in those patients suffering from multiple drug allergies (e.g. from both DDS and thiambutosine allergy), and together with the established second-line anti-leprosy drugs, in those patients who develop DDS allergy. Similarly, it may be considered for any previously-untreated leprosy patient, in whom for any reason dapsone is contra-indicated.

Because of its anti-inflammatory action as well as its anti-leprosy action, treatment with G 30 320 may be considered in the various types of reactions in leprosy and in acute nerveswelling and nerve pain. In erythema nodosum leprosum, unless the reaction is so mild that it can be easily controlled with the standard anti-reaction drugs (antimony compounds, antimalarials, and mild anti-inflammatory drugs) treatment with G 30 320 should be seriously considered; the other alternatives are dapsone plus steroids, or dapsone plus thalidomide. In non-lepromatous lepra reactions, and in previously untreated non-lepromatous leprosy where it is feared that nerve damage may develop on dapsone therapy, treatment with G 30 320 should be considered as an alternative to dapsone plus steroids.

DOSAGE

G 30 320 is given orally, and is available in capsules of 100 mg. The dosage should be adapted to circumstances. In untreated patients with lepromatous leprosy, who receive G 30 320 as their first anti-leprotic drug, 100 mg 3 times a week seems adequate, provided that no ENL has as yet appeared. On the other hand, in sulphone-resistant patients with active leprosy, the minimum recommended dose is 100 mg 6 times a week. These figures apply to patients weighing 40 to 60 kg.

In ENL or in reactions in non-lepromatous leprosy, the individual dose required just to suppress the reaction should be determined. A possible procedure would be to give the patient 200 mg/day for 3 weeks; if at the end of that time the reaction is not controlled, then the daily dose should be increased by 100 mg; if, on the other hand, it is controlled, then the daily dose should be slowly decreased. An increase in the daily dose should not exceed 100 mg in any one week, and as soon as inflammatory signs are under control the dosage should not be increased further. In general, it is suggested that the dosage should not exceed 400 mg/day. There may be a very few patients whose reactions are not controlled even on this dose, and such patients require admission to hospital and careful clinical observation. In such circumstances, under direct medical supervision, the dose could be increased to 500 or even 600 mg/day for a short period or, alternatively, a second anti-inflammatory agent could be introduced. Combined treatment will probably prove to be necessary only in exceptional cases.

Once the reaction has been brought under control, treatment with G 30 320 should be continued for a considerable period; in ENL. this will probably be for at least 6 months, Decrease in dosage should be slow in every case, e.g. by 50 mg/day, and waiting 3 weeks before a further reduction is made. Thus, a patient controlled on 200 mg/day could have his dose reduced to 200 and 100 mg on alternate days; if after 3 weeks no relapse of the reaction has occurred, then the dose may be further decreased to 100 mg daily.

Chronic reactors, or patients who are already in reaction when it is decided to give them G 30 320, are often already receiving steroid treatment. In such patients, the steroid treatment should be continued until the reaction is fully controlled on the appropriate dose of G 30 320. Although it is difficult to give general recommendations, once a patient has been free of reactions for about one month, an attempt may then be made to reduce slowly the dose of steroid. Any relapse of the reaction may then be countered, not by an increase of the steroid dosage but by temporary increase in the dosage of G 30 320, although the needs of each patient must be considered individually. Once the patient requires no further steroids and is stablized on G 30 320, then the objective is to reduce slowly the dose of the latter drug until the base line dosage for reaction patients of 100 mg of G 30 320 6 times a week has been achieved.

M. F. R. WATERS.

CHEMICAL FORMULA AND STRUCTURE

Lampren (G 30 320; B 663) is 3-(p-chloroanilino)-10-(p-chlorophenyl)-2,10-dihydro-2-(isopropylimino)-phenazine, formula $C_{27}H_{22}Cl_2N_4$, with the following structure:



Patterns of Neurological Involvement in Relation to Chronic And/Or Recurrent Erythema Nodosum Leprosum

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Comparative tests of the motor and sensory functions of 3 peripheral nerves, ulnar, median, and lateral popliteal, in leprosy patients with and without erythema nodosum leprosum (ENL), revealed much greater loss of peripheral nerve function, particularly sensory function, in the patients with recurrent or chronic ENL than in those without ENL. The pathogenesis of the phenomenon is discussed.

Erythema nodosum leprosum (ENL) is a serious complication occurring during the clinical course of bacillated forms of leprosy, most commonly in lepromatous leprosy. Both the pathogenesis and clinical significance of ENL are ill-understood. The Committee on Classification at Madrid Congress (1953) suggested that "erythema nodosum leprosum is usually of good prognostic value". Wolcott (1947) presented evidence which demonstrated that there is a relative delay in clearance of bacilli in the "reaction group" who tend to take longer to become negative. He states: "We see clear evidence that erythema nodosum leprosum is detrimental to the patient". This view is also supported by Davison and Kooij (1957). These studies on the effect of ENL on the course of the disease have been mainly concerned with the bacteriological aspects of leprosy and make no reference to the neurological status of the patients following recurrent episodes of reaction.

It is generally accepted that ENL is accompanied by an acute inflammatory process occurring in tissues in which there are lepra bacilli (Ridley, 1960). Since the major target tissue in leprosy is the nerve, it would appear probable that this "reaction" could adversely affect peripheral nerves.

In order to test this hypothesis, therefore, a study of peripheral nerve functions was carried out in 33 patients with recurrent ENL and in a second group of patients with lepromatous leprosy but without ENL or acute neuritis who were receiving regular treatment with DDS, and who served as a control.

MATERIAL AND METHODS

In all, 66 ulnar, 66 median and 66 lateral popliteal nerves in 33 adult patients with a history of recurrent and/or chronic ENL were studied. All the patients had lepromatous leprosy with a history of 6 or more episodes of ENL, the maximum number of episodes being

40 and the average 10. Among this group, acute painful neuritis occurred at the time of ENL with a frequency varying from nil to 18 times, and an average of 4 episodes over a 36-month period. These patients were admitted to the Schieffelin Leprosy Research Sanatorium between 1964 and 1967 for treatment of "reaction" and were followed up for a minimum period of one year. These 33 patients were matched with the control group in relation to age, sex, duration of the disease and bacterial index (B.I.). In all cases peripheral nerve function was tested by (a) manual muscle tests, using the Medical Research Council grading scale; and (b) charting of sensory areas in the upper and lower limbs, using No. 5 nylon-thread applicators.

Patients in the ENL group were available for more intensive study of peripheral nerve function as they were admitted to hospital during periods of "reaction". Peripheral nerve integrity was therefore further assessed in these patients on the basis of strength duration curves which were recorded at 3-month intervals, using a RAF-type II electronic stimulator.

During the acute phases of exacerbation of ENL and acute painful neuritis specific antileprosy treatment was stopped and antiinflammatory drugs such as prednisolone, chloroquine, and parenteral antimony were given to control the reaction. Specific therapy was resumed when the entire reactive process was under control, usually 6 to 12 weeks after the acute episode.

RESULTS

Peripheral nerve function as recorded by manual muscle tests on the muscles supplied by the ulnar, median, and lateral popliteal nerves showed that there was a significant difference between the ENL group and the control group.

Thus, deterioration in function was observed in 12 ulnar nerves out of a total of 66 in the ENL group (18%), whereas in the control group only 3 nerves (4.5%) appeared to be adversely affected.

In regard to the median nerve, 6 out of 66

(9%) deteriorated in the ENL group and no damage was recorded in the control group; while deterioration in the lateral popliteal nerve was observed in 5 out of 66 (7.5%) and 1 out of 66 (1.5%) in the ENL and control groups respectively (see Table 1).

TABLE 1 Peripheral nerve function

		ENL gr	roup	Control grou		
Nerve	No.	No. affected	%	No. affected	%	
Ulnar	66	12	18	3	4.5	
Median	66	6	9	0		
Lateral popliteal	66	5	7.5	1	1.5	

The greatest deficit in motor function was recorded in the ulnar nerve in both the ENL (18%) and non-ENL groups and was statistically significant.

Progressive loss of sensory function as recorded by increase in the area of anaesthesia in the limbs was much more frequent and significant than the changes recorded in motor power by the manual muscle tests. Thus,

TABLE 2 Increase in anaesthesia in 66 upper and lower limbs

	Uppe	er limb		Lower limb								
ENL	group	Contro	l group	ENL	group	Contro	l group					
No.	%	No.	%	No.	%	No.	%					
51	76.5	7	10.5	52	78	8	12					

51 patients out of a total of 66 (76.5%) showed an increase in area of anaesthesia in the upper limb in the ENL group as compared with 7 out of 66 (10.5%) in the control group, while in the lower limb 52 out of 66 (78%) showed an increase in the area of anaesthesia in the ENL group as compared with 8 out of 66 (12%) in the control group (Fig. 1).

Strength duration curves recorded for the ENL group showed deterioration of nerve function in a slightly larger proportion of the patients than was recorded by the manual muscle test (Table 3).





Worsening of peripheral sensory loss (a) in left arm and (b) in left leg in patients with recurrent erythema nodosum leprosum is shown; shaded portions, areas anaesthetic to No. 5 nylon; stippled portions, area showing mis-reference.

TABLE 3

Deterioration in ENL group—strength duration curves (S.D.) and manual muscle tests (M.M.)

Nerve	S.D. curve	M.M. test
Ulnar	19.5%	18%
Median	15.5%	9%
Lateral popliteal	10.5%	7.5%

DISCUSSION

From the data presented it appears obvious that, on the whole, erythema nodosum leprosum adversely affects peripheral nerve function, both motor and sensory. There was no direct correlation between any of the various antiinflammatory drugs used in the ENL group to control the "reaction" and the change in nerve function. The serial strength-duration curves obtained from the patients in the ENL group appeared to be a reliable, objective method of detecting neurological deficit before clinical evidence of muscle weakness became apparent.

The exact pathophysiological process which results in the deterioration of nerve function is not clear. It is likely that during the ENL episode there occurs an acute inflammatory exudate in the nerve similar to that in the skin lesions of ENL (Job and Bhaktaviziam, 1967) and in the joints (Karat et al., 1967). The resultant oedema may cause neuropraxia in the acute phase followed by healing by fibrosis and scarring, which may contribute to destruction of nerve fibres and loss of nerve function. In a significant number of cases, the inflammatory response in the nerve may be very intense and may progress to abscess formation (ENL lesion of nerves) and destruction of nerve fibres. Though such a nerve lesion in lepromatous leprosy is thought to be uncommon, at the Schieffelin Leprosy Research Sanatorium during the last 6 months we have demonstrated such an abscess in 4 nerves in patients with lepromatous leprosy in reaction both at operation and by histological examination of the specimens of nerve obtained at surgery out of the 7 randomly explored, painfully enlarged, nerves during "reaction" (Figs 2 and 3). Clinically, there was a close relationship between abrupt onset of painful swelling of the ulnar, median or lateral popliteal nerves during ENL and the occurrence of "nerve abscess" in this group.

We have also observed a "vasculitis" of smaller blood vessels during severe reactions and confirmed this by histological examination. Typically there is proliferation of the endothelium, along with infiltration of all coats of the vessels with polymorph leukocytes. The endothelial cells are packed with large numbers of acid-fast bacilli. Vasculitis of this kind involving the vasa nervorum may cause



FIG. 2 Photomicrograph to show nerve abscess (H & E $\times 30).$

FIG. 3 Photomicrograph to show acute inflammatory exudate consisting of polymorphs and macrophages ((a) H & $E \times 120$; ((b) H & $E \times 400$).

Fig. 2





Fig. 3 (a)

diminution of the blood supply to the nerve and consequent nerve damage.

Considerable data have been presented to suggest the possibility of an antigen-antibody reaction of hypersensitivity type or autoimmune type as one of the aetiological factors in the pathogenesis of "reaction" in leprosy (Ingram and Brain, 1957; Ridley, 1960). It is conceivable that the peripheral nerves, being the "target tissue" in lepromatous leprosy, may participate in this type of immunological reaction, to the detriment of the integrity of their function.

SUMMARY

In 33 patients with recurrent or chronic ENL a study of the ulnar, median and lateral popliteal nerves showed statistically significant deterioration in their motor and sensory function when compared with that in a carefully matched group of patients who did not develop ENL and were receiving regular, continuous treatment with DDS. Deterioration in sensory function in these patients was more marked than deterioration in motor power as recorded by the manual muscle test.

The pathogenesis of the production of nerve

deficit in patients with recurrent reaction is discussed.

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Second Trial of Low Dosages of DDS in Lepromatous Leprosy

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Three small groups of patients with lepromatous leprosy were treated for 21 months with a low dosage of DDS, receiving respectively 250, 50, and 20 mg of the drug weekly. In all groups the percentage of infiltration and the bacteriological index decreased, as did also the percentage of fragmented bacilli, and in most cases after one year 90% of the bacilli had become granular. No patient became bacteriologically negative. The frequency of lepromatous reactions remained unchanged in the 2 groups receiving the higher doses, and increased in the group given 20 mg weekly. It is suggested that a weekly dosage of 200 mg of DDS should be adequate for uncomplicated lepromatous leprosy.

A previous study by the authors (Leiker and Carling, 1966) suggested that a dosage of 200 or 400 mg of DDS weekly was not significantly less effective than one of 600 to 800 mg weekly. In the present study 3 groups of lepromatous patients (14 in all) were treated for 21 months with DDS, 3 of them receiving 250 mg weekly (Group 1), 5 a dose of 50 mg (Group 2) and 6 one of 20 mg of the drug weekly (Group 3).

All the patients were clinically, bacteriologically and histologically lepromatous. Most of them had received previous treatment, but all were still strongly bacteriologically positive when the trial was started. At the beginning of the trial and then every 3 months thereafter smears were taken from 6 sites and examined locally. The bacteriological indices are shown in Table 1.

In addition biopsy specimens were taken every 3 months, each time from the same lesion, near to but just avoiding the scar of previous biopsies. These specimens were assessed blindly, the dosage group to which the patient belonged being unknown to the investigator. Assessment was based on the percentage of sections occupied by infiltration, the bacterial index (B.I.), the percentage of morphologically intact bacilli, the percentage of fragmented bacilli, and the percentage of granular bacilli. Deeply and evenly stained bacilli were recorded as intact and regarded as alive. Bacilli showing a slightly irregular staining but not broken up by unstained parts were recorded as fragmented-a proportion of these bacilli may still have been alive. Bacilli which were broken up into a number of granules were recorded as granular and were regarded as being dead. The results of examination of the biopsy material are shown in Table 2. The frequency of lepromatous reactions occurring during the 2 years immediately before the trial and also those during the trial was recorded; the numbers are shown in Fig. 1.

RESULTS

In all 3 groups the percentage of infiltration decreased, the average decrease being 15% per annum. The differences between the groups in this respect are not significant.

In all groups the B.I. decreased significantly, the decrease being about 1.0 per annum. This is about the same rate of decrease as has been found elsewhere in patients receiving 600 mg of DDS weekly. In the patients treated with 20 to

									Total dosage	e No. of reactions				
				Mo	nths				DDS	Last 2 years	During			
	0	3	6	9	12	15	18	21	(g)	before triul	trial			
Group I—	-250 mg	DDS weel	kly											
2007	1.65	2.15	1.65	0.83	(0.83)	0.83	0.5	0.6	27.35	0	0			
2192	5.0	4.0	3.50	3.50	2.50	3.50	3.1	3.1	22.35	0	0			
2120	5.0	5.0	3.65	4.50	3.80	4.00	4.1	4.l	23.35	0				
Average	3.9	3.7	2.9	2.9	2.4	2.8	2.6	2.6	24.4	Total 0				
Group 11-	-50 mg	DDS weel	kly											
2053	2.85	3.30	3.85	2.83	3.5	3.0	1.6	1.3	8.35	0	2			
2057	2.85	3.85	3.35	2.66	2.5	1.1	1.5	1.1	8.80	0	0			
2006	2.50	2.65	1.85	1.60	0.8	0.5	0.5	0.6	8.35	2	0			
2000	1.15	2.00	1.15	1.30	1.1	0.8	0.6	0.3	8.89	0	0			
2158	2.50	2.50	1.85	1.50	1.1	0.6	0.5	0.5	9.15	0	0			
Average	2.4	2.9	2.4	2.0	1.8	1.2	0.9	0.8	8.7	Total 2	2			
Group III	-20 mg	DDS we	ekly											
2067	3.65	4.0	4.0	3.5	3.1	3.6	3.0	2.6	2.6	0	1			
2043	1.00	1.15	1.5	1.16	0.8	0.3	0	0	2.6	1	0			
2150R	3.30	3.50	3.35	3.60	3.3	3.3	2.0	2.8	2.0	1	4			
2137R	4.50	4.50	3.80	3.83	2.8	4.8	4.0	(4.0)	5.0	1	5			
2008R	2.85	2.85	2.15	2.16	1.2	1.5	1.0	0.5	4.39	2	4			
2003R	2.65	3.65	3.35	2.66	2.0	2.1	1.6	1.5	2.15	7	7			
										frequent				
Average	3.0	3.3	3.0	2.8	2.2	2.6	2.0	1.9	3.12	Total 12	21			

 $$T_{\rm ABLE}$\ l$$ Bacterial index in smears taken at 3-monthly intervals

Not included—2246, after 5 months of treatment (B.I. 25 to 5) continuous reaction (borderline tuberculoid lesions) steroid dependent, trial stopped.

2248, abandonment after 9 months.

R, Repeated reactions.

(), No biopsy taken, figures refer to last biopsy.

50 mg of DDS weekly the decrease was on the average slightly less in the 2nd year of treatment than in the 1st year.

As most patients had received previous treatment the percentage of intact bacilli was already low at the beginning of the trial. In only one patient a few intact bacilli, accompanied by an increase in the percentage of fragmented bacilli, reappeared after 15 months of treatment. This patient had received 300 mg of DDS weekly.

In most patients the percentage of fragmented bacilli began to decrease during the first 3 months of treatment and in all groups a marked decrease was seen in the second 3 months. In most patients in all 3 groups 90% or more of the bacilli had become granular after one year of treatment. Further increase in the percentage of granular bacilli was slower in all groups. However, none of the patients had become bacteriologically negative at the end of the trial.

Groups 1 and 2 showed no significant difference in frequency of lepromatous reactions before and during the trial, but in Group 3 the frequency of reactions increased during the trial.

		0		,								1	Mont	hs				0		
	A	Onse B	et of C	trial D	E	A	B	C^{3}	D	E	A	B	$\overset{6}{C}$	\overline{D}	E	A	B	C^{9}	D	E
							Groi	ıp I-	-250) mg	DDS we	ekly								
2007	60	5	0	43	57	40	5	0	58	42	40	4	0	13	87	50	3.5	- 0	6	94
2192	30	5	0	66	34	50	6	0	71	- 29	30	5	0	32	68	30	5	- 0	21	79
2120	20	6	0	41	59	15	5.5	0	31	69	15	5	0	31	69	10	5	0	18	82
Average	37	5.3	0	50	50	35	5.3	0	53	47	28	4.7	0	25	75	30	4.5	0	15	85
							Groi	ıp H	50) mg	DDS we	ekly								
2053	40	5	0	42	58	60	5	0	31	69	55	5	0	27	73	50	5	0	13	87
2057	30	6	1	44	55	40	5	0	64	36	30	5	0	36	64	25	5	0	27	73
2006	20	5	0	27	73	20	6	0	25	75	40	4.5	0	18	82	35	4	0	9	91
2000	30	4	0	35	45	50	4	0	19	81	30	3.5	1	9	90	50	1.5	0	30	70
2158	15	4	0	22	78	20	4	2	19	79	15	4.5	0	19	81	10	3	0	5	95
Average	27	4.8	0.2	38	62	38	4.8	0.4	32	68	36	4.5	0.2	21	79	34	3.7	0	17	83
							Grou	p II	I = 2	0 m g	y DDS we	eekly								
2067	20	6	0	50	50	40	6	0	32	68	40	5	0	30	70	50	5	0	12	88
2043	60	5	0	14	86	80	4	0	9	91	50	4	0	4	96	80	3	0	1	99
2150R	50	5	0	28	72	60	6	0	42	58	50	5	0	21	79	50	5	0	5	95
2137R	30	6	0	55	45	40	6	0	52	48	50	6	0	25	75	20	5	0	25	75
2008 R	-10	6	1	44	55	10	6	1	43	56	15	5	0	29	71	15	4.5	- 0	13	87
2003R	40	5	0	51	49	20	5	0	37	63	30	5	0	21	79	25	5	0	10	-90
Average	35	5.5	0.2	40	60	42	5.5	0.2	36	64	39	5	0	22	78	40	4.6	0	11	89
									M	onth	8								_	
	A	B	$\frac{12}{C}$	D	E	A	B	$\begin{array}{c} 15\\ C\end{array}$	D	E	A	В	$\frac{18}{C}$	D	E	A	B	21 C	D	E
							Grou	p I-	-250	mg	DDS we	ekly								
2007	40	2.5	0	2	98	30	2	1	24	75	30	1.5	1	12	87	30	1	- 0	- 0	100
2192	25	4	0	16	84	25	3	0	5	95	40	2	0	9	91	20	1	0	2	98
2120	10	5	0	11	89	10	5	4	9	91	15	5	0.7	7	93	15	4.5	0	6	94
Average	25	3.8	0	10	90	22	3.3	0.3	13	87	28	2.8	0.3	9	91	22	2.2	0	3	97
							Grou	p II	—50	mg	DDS we	ekly								
2053	60	4.5	0	6	94	50	4	0	3	97	40	5	0	4	96	25	5	0	4	96
2057	20	5	0	5	95	15	5	0	12	88	20	5.5	0	17	83	20	5	- 0	8	92
2006	50	4.5	0	9	91	40	4	0	4	96	45	4	0	10	90	20	2	0	2	98
2000	50	2	0	12	88	40	2	0	15	85	60	2	0	23	77	20	2	0	2	98
2158	10	2	0	1	99	15	2	0	6	94	15	2	0	7	93	5	$\frac{2}{2}$	- 0	- 0	100
Average	38	3.8	0	7	93	32	3.4	0	8	92	36	3.7	0	12	88	18	3.2	0	3	97
							Grou	p II	I—20) mg	DDS we	ekly								
2067	30	5	0	14	86	10	4.5	0	7	93	5	4	0	6	94	10	4.5	0	4	96
2043	70	2	0	1	99	5	2	0	1	99	15	2	0	2	98	25	1.5	- 0	2	98
2150R	45	5	0	7	93	40	5	0	9	91	40	5	0	7	93	50	4	- 0	$\frac{2}{2}$	98
2137R	20	5	0	16	84	15	5	0	22	78	(15	5	0	22	78)	(15	5	0	22	78)
2008R	10	4	0	2	98	10	4	0	1	99	10	4	0	1	99	5	4	0	1	99
2003R	10	2	0	1	99	10	3.5	0	7	93	10	2	0	4	96	10	2	0	0	100
Average	31	3.9	0	7	93	15	4	0	8	92	16	3.7	0	7	93	20	3.5	0	5	95

TABLE 2 Results of biopsies at 3-monthly intervals

A, proportion of of section occupied by infiltrations; B, bacillary index; C, percentage of intact bacilli; D, percentage of fragmented bacilli; E, percentage of granular bacilli; R, repeated reactions. (), no biopsy taken, figures refer to last biopsy.



Low dosage of DDS. Group 1, 250 mg, Group 2, 50 mg, Group 3, 20 mg of DDS weekly.

DISCUSSION

The number of patients in the trial was admittedly small. The frequency of detailed observations, however, was high. The bacteriological changes in most patients of all groups showed basically the same trend.

All patients improved during the trial. This improvement, however, cannot be entirely ascribed to the activity of the drug. The shift from fragmented bacilli to granular bacilli and the decrease in the B.I. were probably to a large extent due to removal of dead bacilli from the tissues by the body itself and not due to the effect of the drug. It is, however, significant that during 15 months of treatment intact bacilli did not reappear in any of the patients treated with the lower dosages of DDS, and that after 15 months only a few intact bacilli appeared temporarily in a few patients who had shown frequent reactions. This suggests that even these low dosages do inhibit the multiplication of bacilli. The slightly slower decrease in the percentage of fragmented bacilli found in the first 6 months in the groups treated with 20 and 50 mg of DDS weekly, as compared with the group given 250 mg weekly, suggests that the lower dosages are somewhat less effective than the higher. Until further trials in untreated lepromatous patients or patients with a higher percentage of intact bacilli have produced more information about the exact degree of efficacy of the lower dosages it seems wise to regard a dosage of about 200 mg of DDS weekly as adequate for patients with uncomplicated lepromatous reactions. In patients with frequent reactions the lower dosages may be used, as they are doubtless still efficacious, although the bacteriological effect is possibly not optimal.

In this trial the frequency of reactions was highest in patients receiving the lowest dosage of DDS. This is not surprising because 5 out of the 6 patients in this group had already shown reactions before the trial and the tendency to becoming reactive frequently increases when sulphones, even in a lower dosage, are continued. The outcome of this trial does not show that patients who are intolerant of a high dosage of sulphones will necessarily tolerate a lower dosage. It is possible that patients who have not yet become truly sensitized to sulphones may benefit from a lower dosage, but it is doubtful if the real problem cases will do so in regard to frequency of reactions.

The 4 patients who had frequent reactions while receiving 20 mg of DDS weekly improved bacteriologically, no intact bacilli reappearing in any significant numbers. There is, however, a danger that, although the number of bacilli in the infiltrates, which can be easily demonstrated by skin smears and skin biopsies, declines, the bacilli which may be concealed at as yet unidentified sites are not killed by a low dosage of DDS. Such bacilli may become resistant to the drug. The fact that lepromatous patients who have been treated with a higher dosage of DDS not infrequently relapse when treatment is withdrawn soon after skin smears and biopsies have become negative is regarded as evidence that such hidden foci of living bacilli exist and that these bacilli are not easily killed by treatment.

The present trial has not produced a final answer to the question of the most effective dosage of DDS. There is still an urgent need for more detailed studies on the optimal dosage of sulphones.

SUMMARY

(1) Three groups of lepromatous patients were treated respectively with 250, 50 or 20 mg of DDS weekly for 21 months.

(2) Bacteriological progress was assessed by examination of 3-monthly smears and by serial biopsies, each time from the same lesion.

(3) All patients improved bacteriologically. The differences in bacteriological progress between the groups were not marked. It is possible that 250 mg of DDS weekly is slightly more effective than the lower dosages. (4) The frequency of reactions was not significantly lower in patients treated with the lower doses. The highest frequency of reactions was found in patients treated with the lowest dosage but several patients in this group had already shown frequent reactions prior to the trial.

(5) The decrease in bacillary index cannot be ascribed entirely to the effect of the drug, but is partly due to removal of dead bacilli by the body itself. The fact, however, that intact bacilli did not reappear suggests that very low dosages are effective.

(6) Relapse was frequently seen when treatment was stopped soon after smears and skin biopsies had become negative, suggesting that there were hidden foci of living bacilli. As it is not certain that such bacilli too are killed **by** low dosages and drug resistance may develop, it is suggested that about 200 mg of DDS weekly may be regarded as an adequate dosage for patients with uncomplicated lepromatous leprosy, until further evidence for the efficacy of lower dosages is shown.

REFERENCES

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A New Approach to the Problem of Grossly Deformed Feet

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Many leprosy patients suffering from breakdown of the bony architecture of the foot have undergone below-knee amputation with reasonably satisfactory results. However, to avoid the loss of so much tissue the authors have devised a modification of the old Pirogoff amputation. In this, half the calcaneum is preserved and the stump arthrodesed into the ankle mortice, thus giving a weight-bearing heel and a leg little shorter than normal and capable of accepting a simple stump boot. The operation is described in detail.

Over the last 5 years we have received at this hospital a trickle of crippled leprosy patients redirected from various leprosaria where it is known that we have facilities for fitting



FIG. 1 Patient no. 4 before operation.

*Present address: Moorshead Memorial Christian Hospital, G. Udayagirs, Phulbans District, Orissa, India. artificial limbs. All of them had suffered gross tissue loss and complete breakdown of the bony architecture of the foot (Fig. 1), and below-knee amputation had been considered reasonable treatment. These patients have been pleased with the result, this arising no doubt from their relief at the loss of a foot that had produced only sinuses and offensive discharge for years. Many of these patients were destitute, and even the possession of a prosthesis that originated in New York or Roehampton contributed to the glow of pleasure with which they walked away. But to us there has always been an uncomfortable feeling that something less in tissue loss should be possible, for there is no comparison here with the diabetic or thrombo-angiitic type of patient, for whom below-knee amputation is correct and in fact inevitable.

THE MODIFIED PIROGOFF AMPUTATION

Our experience with definitive surgery in bones distorted by chronic osteomyelitis encouraged us to aim at an end-bearing stump, while keeping the leg as near normal length as possible. We have found that osteotomies of the femur in bones that have been riddled with osteomyelitis have not produced flare-ups if reasonable precautions are taken, and bony union has been good. In our leprosy patients we have attempted retropulsion of the foot in cases where destruction of the calcaneum has produced a boat-shaped foot. In such cases either an excision of the talus or a modified triple arthrodesis through the most unpromising tissues has healed well.

In the past the standard operation has been the conventional or modified Syme's amputation (Fig. 2 (a) and (b)); this shortens the leg by 6.25 to 7.5 cm $(2\frac{1}{2}$ to 3 in.) and has also made it difficult to fit a good prosthesis or stump boot. The Pirogoff amputation (Fig. 2 (d)) has fallen into disuse. In this procedure the malleoli were sawn off just above the ankle joint and a small piece of the calcaneum retained in the dorsal flap was brought to lie across the cut surface of the tibia and fibula. However, this again resulted in a stump as short as in the original Syme's operation. Such a patient can only walk in emergency without a boot.

In the cases we have completed, about half the calcaneum has been preserved in the flap and the ankle mortice denuded of cartilage for the calcaneal stump to be arthrodesed in it (Fig. 2 (c)). We expected trouble with the blood circulation in this much larger than normal flap, but in only one patient has gangrene occurred, and even here it was limited and of late occurrence. We drive a Steinmann pin through the heel during the operation and under direct vision (Fig. 3); this holds the arthrodesis firmly and facilitates suture of the flaps. No attempt is made to trim the lateral bulges which appear in suturing this flap, as this would further jeopardize its circulation. The bulges tend to shrink (Fig. 4) and can always be trimmed later. We have observed minor delay in healing, due to haemorrhage, but no sepsis. When the bone unites, the patient is left with a weight-bearing heel only 1.25 to 2.5 cm $(\frac{1}{2}$ to 1 in.) shorter than normal (Fig. 4). This means that a simple stump boot can be made without the considerable build-up which rendered the conventional prosthesis unstable. Since devising this operation, we have discovered in an old edition of Modern Operative Surgery edited by Grev Turner (1943), a procedure described as Watson's operation, in which the whole calcaneum was retained and arthrodesed into the ankle joint. However, the operation was mentioned only to be condemned!



(a) Syme amputation;(b) modified Syme;(c) present operation;(d) Pirogoff;(e) stump compared with normal foot.



Patient no. 4 immediately after operation. Note Steinmann pin and flap "bulge".



FIG. 4 Patient no. 1. Note minimal shortening and shrinkage of lateral bulges.

METHODS

A tourniquet is used throughout the operation. It is wise to cut the skin flap generously, for it can be trimmed finally if too large, and it is easy to underestimate the length required. The incision is carried down to bone, the ankle joint opened, and the foot dislocated in extreme plantar flexion. Attention is now paid to the ankle mortice, which must be completely denuded of cartilage. The forefoot and tarsus are separated and the calcaneum fashioned to fit into the ankle. Each case has to be treated individually in this tailoring process, for in each the degree of disorganization varies. In some cases the Achilles tendon has had to be carefully divided to allow the calcaneum to move freely. It is emphasized that the calcaneal remnant remains attached to the dense fibrous pad of the heel and is rotated into the ankle mortice by moving up the heel flap. This ensures the minimum interference with the blood supply. After insertion of a Steinmann pin, if desired, the skin flaps are closed without drainage, the pressure of a firm dressing being sufficient to control haemorrhage. The sutures are removed after about 14 days, and walking with crutches is allowed. Weight-bearing, however, should be delayed for 2 months to allow bony union to occur.

Details of the stump boot are as follows. The patient with the beggar mentality may soon discard any boot given, and with this operation he will be able to move about with little discomfort or awkwardness of gait. However, a simple boot can be made to prevent the development of ulceration of the stump. This incorporates a build-up of wood 1.25 to 2.5 cm $(\frac{1}{2}$ to 1 in.) thick and lined with microcellular rubber. A slight roll on the sole, using a portion of old car tyre, will make for easier ambulation. If the patient wishes for a more sophisticated boot, a mould of the foot can be taken and from this a moulded sole and build-up of cork can be made. This utilizes more of the surface area of the stump for weight-bearing, thus decreasing the risk of ulceration. A Plastizote mould may also be very easily utilized, but whether it is strong enough to withstand the shearing and compression forces to which it may be subjected is not yet proved.

ILLUSTRATIVE CASES

Patient 1. S. Male, aged 46 yr. The operation was conceived for a patient with thromboangiitis obliterans in whom gangrene was limited to the toes of the right foot. Lumbar sympathectomy had previously been performed. In spite of the vascular condition the blood supply to the flap proved to be adequate, and this encouraged us to proceed with further patients.

Patient 2. P. N. Male, aged 48 yr. Hansen's disease, tuberculoid type. This patient had anaesthesia of both lower legs with gross disorganization of the left ankle joint of the Charcot type.

Patient 3. S. S. Male, aged 38 yr. Hansen's disease, tuberculoid type. Severe deformity of all limbs. Median, ulnar and radial paralysis of the left hand; median and ulnar paralysis of the right hand, left foot-drop with osteomyelitis of the forefoot and shortening of the foot, and severe disorganization of the right foot, but no sinuses. He was referred from another hospital for right below-knee amputation. Instead of

this, however, a modified Pirogoff amputation was performed. At operation, the tarsal bones were fused to the tibia, and an ankle mortice had to be created with a chisel into which the the calcaneum could be fitted. The Achilles tendon had to be divided before the flaps could be brought together with some tension.

Patient 4. K. N. Male, aged 55 yr. Hansen's disease, tuberculoid type. This patient had undergone below-knee amputation of the left leg some 25 years previously and a peg-leg type of prosthesis had been fitted. The right foot became increasingly deformed, with inversion, reversal of the longitudinal arch, and gross lateral border ulceration. This was initially treated by excision and grafting of the ulcer;

this healed rapidly, and a fitted boot was supplied. Small recurrences occurred on the weight-bearing area and it was decided that removal of the ulcerated forefoot would cause no greater disability, in spite of the amputated left leg. A modified Pirogoff amputation was therefore performed.

SUMMARY

A technique of osteoplastic amputation through the ankle-joint is described, which has been found useful in the treatment of the disorganized feet of leprosy patients. A weightbearing stump of near normal length results, and this is a distinct advantage where expertly made prostheses may not be available.

A Positioning Splint for Use in Tendon Transplantations for Drop Foot

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Details are given of a simple but ingenious splint devised by the author for use in the operation for correction of drop foot. The splint is designed to maintain the patient's foot in a fixed degree of dorsiflexion and in a true plantigrade position and so avoid undue tension on the tendon suture.

One of the difficulties experienced in the course of the operation for correction of a foot drop is the adjustment of the tension of the tendon in such a way that the same tension is reproducible in subsequent operations. Usually the foot is maintained in dorsiflexion by an assistant during the suturing of the transplanted tendon. This is not very satisfactory, however, as the foot may inadvertently be tilted into either inversion or eversion without this being noticed in time; or if the assistant tires during the latter part of the operation, the foot may be allowed to relax and thus put too much strain on the tendon suture.

The splint described in this paper was designed to deal with both these difficulties by maintaining the foot in a fixed degree of dorsiflexion and in a true plantigrade position with reference to inversion-eversion. In this position suture of the tendon can be carried out and the tension measured by the length of tendon pulled distally from the neutral or relaxed position. In the prototype of this splint we initially made the angle of dorsiflexion variable, but in practice we found that, just as in the case of the hand-positioning splint, this was not necessary. In the splint now described, the angle of dorsiflexion is fixed at 70 degrees, and the surgeon is then free to adjust the tension in the tendon in accordance with his own experience.

The splint, which consists of 3 segments, so



Fig. 1

that it can be folded for purposes of sterilization, is made of either aluminium or galvanized iron, and its width is 10.5 cm (4 in.). Each of the 3 segments is 25.5 cm (10 in.) long and the 2 end segments make each an angle of 70 degrees with the middle segment when opened out fully. The average length of a patient's leg is, of course, greater than 25.5 cm, but when the limb has to be draped this procedure is significantly easier if the middle segment is short.

This splint can be made in any reasonably equipped workshop. The one illustrated in Fig. 1 was made for us by Messrs. Hebbar Bros., instrument manufacturers, Palghat, Kerala State, S. India, from whom these splints are obtainable.

New Year Honours

Her Majesty Queen Elizabeth II has been graciously pleased to honour several distinguished workers in the field of leprosy. We offer our congratulations to them, realizing how richly deserved in all cases is this public recognition of a lifetime of service.

Dr. Robert G. Cochrane, F.R.C.P., President Emeritus of the International Leprosy Association, who is already the recipient of the Damien Dutton Award and other international honours, is appointed a Companion of the Order of St. Michael and St. George (C.M.G.) for his services in the treatment and control of leprosy. After 40 years of devoted service throughout the world, notably in India, and in a variety of capacities, Dr. Cochrane has returned with his wife to his work in Tanzania (present address: Kola Ndoto Hospital, Box 46, Shinyanga, Tanzania).

Dr. Margaret Fitzherbert, F.R.C.O.G., is appointed an Officer of the Order of the British

World Health Organization

From the official records of the Proceedings (No. 169), the following information is taken.

Monsieur Jarison (*Madagascar*) (p. 45) referred to the 150,000 leprosy patients newly registered in tropical Africa as the result of the work of mobile diagnostic teams. Fear had hitherto kept many from openly admitting that they had leprosy.

In *India* (p. 50), leprosy continued to pose serious problems, especially in Madras and Andhra Pradesh. W.H.O. stimulates and coordinates research into different aspects of the disease.

Uganda (p. 96) acknowledged the help of W.H.O. in the despatch of a leprosy consultant to assess the present status of leprosy control services and to make recommendations.

The delegate from *Cameroon* (p. 119) admitted that leprosy, a "social" disease, continued to

Empire (O.B.E.). Dr. Fitzherbert gained a great reputation in Ethiopia as a specialist obstetrician and gynaecologist, and now for the past few years has been foremost in leprosy work both in Addis Ababa itself and in the district.

Dr. Katherine M. Young, of the Christian Dispensary, P.O. Dandeldhura, Ex. Off. Baitadi, West Nepal, is accorded the same honour (O.B.E.) by Her Majesty. Dr. Young has been in real and intimate touch with the medical and social problems of leprosy patients for many years, and has devoted herself in sympathetic service to their needs.

Miss M. M. Stone becomes a Member of the Order of the British Empire (M.B.E.). Sister Stone is well-known for her work at Kumi-Ongino in Uganda in connection with the BCG vaccination trial conducted by Dr. J. A. Kinnear Brown, C.M.G., and is one of the co-authors with him of the paper on page 3 of this issue.

cause anxiety, linked as it is with economic underdevelopment.

Kenya (p. 137) requested advice from W.H.O. on a disease that not only brings suffering and crippling to individuals, but also creates administrative problems in the allocation of funds and the determination of priorities.

Ceylon (p. 139) expressed thanks for the services of a W.H.O. consultant who reassessed the leprosy situation. There are 4,413 known cases of leprosy in Ceylon, with 15,000 contacts.

In *Burma* (p. 188), leprosy is a serious publichealth problem, but the Government is placing its hopes on prevention and control and expects the whole country to be covered by its programme in 5 years.

Dr. Payne, Assistant Director-General of W.H.O. (p. 290), referred to the work of W.H.O. in stimulating and organizing a critical appraisal

of the discrepant results of BCG prophylaxis in leprosy in Africa, Asia, and Australasia. *India* (p. 291) requested W.H.O. assistance in conducting research into the subject in Chingleput, Madras State, and also (p. 300) emphasized the importance of training doctors and paramedical workers in leprosy control and rehabilitation of leprosy patients.

Tribute was paid to the Raoul Follereau Foundation by the delegate from *Upper Volta* (p. 300) who undergirded the work of the *Service des Grandes Endémies* in that country.

The Chief Medical Officer, Leprosy (Division of Communicable Diseases of W.H.O.), had followed with great interest the efforts of the Indian and other governments to control leprosy. In Burma, for instance, the number of registered leprosy patients had risen from 12,000 to over 170,000 in a few years. He emphasized the importance of concentrating treatment on patients with lepromatous leprosy, where re-

In the House of Commons, on 27 November, 1968, Mr. David Ennals (Minister of State, Department of Health and Social Security), provided some interesting facts and figures concerning leprosy in the United Kingdom. In reply to questions raised by the Member for Wembley (South), who had referred to a report that an average of 50 people a year were being notified as having contracted leprosy, Mr. Ennals said:

"The majority of persons suffering from leprosy in England and Wales are being treated as hospital out-patients or by their family doctors. The small number who need hospital in-patient care are treated in hospitals for tropical diseases or, occasionally, in general hospitals.

By the end of 1967, 196 patients were reported to have been cured out of a total of 732 notified since 1951. Of the 357 patients remaining on the register at the end of 1967, 196 were known to be quiescent, but treatment was continuing as a precaution against recurrence.

Particulars required to be notified under the Infectious Diseases Regulations do not provide information about the country of origin of the patient. There is no evidence to suggest that any person on the register of notified cases has contracted the disease in the United Kingdom." sources in finance and personnel were limited. Case-holding would always raise difficulties in such a chronic disease as leprosy requiring prolonged treatment for clinical arrest and to prevent relapse. Regarding long-acting sulphonamides, he confessed that results from different centres showed considerable divergencies, and serious side-effects had been reported that would prevent his recommending the drugs at present for mass treatment campaigns.

The delegate from *Afghanistan* (p. 329) reported that his Government was most anxious to set up a leprosy control project in the central part of Afghanistan. He feared that increased travel facilities resulted in spread of the disease. W.H.O. had provided a short-term consultant to assess the situation and had given fellowships and training in leprosy treatment. The expansion of epidemiology laboratory services was also included in the programme.

Leprosy in the United Kingdom

While these numbers give no cause for alarm, they do support the oft-repeated contention that in the United Kingdom leprosy must be considered in the differential diagnosis of any chronic atypical non-irritating dermatosis that does not respond to suitable therapy, and of any unusual peripheral neurological disorder that does not fit into one of the commoner diagnostic pigeon-holes. In all countries, England included, there may be patients still on treatment for "mycotic" patches that have failed to clear up despite the continued application of fungicidal ointments, just as there may be patients with ulnar paresis who have unjustifiably borne the label of "hysteria" for far too long. Medical students and doctors should realize that a geographical history may be more important than a "history of children's complaints" when they are confronted with a native-born Englishman who has spent some time abroad, or an immigrant patient who presents himself in a suburban consulting-room or dermatological clinic.

Book Reviews

Notes on Leprosy, 2nd ed., by DHARMENDRA, M.B.B.S., DIP. BACT. (LOND.). Ministry of Health, Government of India, 1967. 408 pages. Price: 58s. 4d.

We extend a warm welcome to the second edition of Dr. Dharmendra's *Notes on Leprosy*, which has now been published. It is extremely good value for the price, and we predict that it will prove even more popular than the first edition, published in 1960.

The book has been completely rewritten, and bears on every page the marks of careful editing and judicious choice of new material. It is definite—even dogmatic—in tone, which is not an undesirable feature in a book intended as a manual for students and nonspecialist practitioners. It carries the impress of the author's wide experience and detailed knowledge of the range of clinical leprosy as seen in India, and the 110 pages of illustrations—some of them in colour, and now interspersed with the text (surely an improvement)—add considerably to the value of the book as a teaching aid and as a work of reference.

Doctors in India who have the privilege of learning their leprosy at Chingleput or Calcutta, will find in the pages of the new Dharmendra all they need to know and more—when confronted by problems of diagnosis and management. They will also, we hope, be stimulated to develop standards of careful clinical observation and wide-awake awareness. Although in the future major advances in leprosy will probably come from laboratory investigations in the fields of experimental microbiology and immunology, there remain problems of transmission and epidemiology to which answers may be found by the painstaking field worker.

Faced with the need of undiagnosed and untreated thousands, in India and elsewhere, the doctor who knows his "Dharmendra" and who follows the practical advice on survey, education and treatment given in its pages, will be able competently to organize a leprosy control scheme, with the right emphasis on diagnosis and treatment and rehabilitation. The dimensions of the leprosy endemic in countries like India, confronted by major killing diseases and uncontrolled population growth—with concomitant undernutrition—serve to emphasize the urgent need to discover effective ways of preventing leprosy. BCG and dapsone prophylaxis point the way, but, as Dr. Dharmendra indicates, there is still a real need for convincing evidence that any measures advocated will achieve their object.

Meanwhile, we advise leprosy workers everywhere to

buy this book and to use it. They will find that a second edition twice the size of the first may be more than twice as useful.

Leprosy for Practitioners by S. J. YAWALKAR, M.D. (MUNICH), D.V.D. (BOMBAY) (LONDON). English Universities Press, 1969. 120 pages. Price: 40s.

The aim of the author of this slim volume is to present the salient facts about leprosy to non-specialists, particularly medical undergraduates and busy general practitioners. Intended originally for the doctor working in India, it is now published in London.

The book shows evidence of an Indian—and even of a Bombay—background, and the standpoint on such questions as classification, pathogenesis, therapy, maculo-anaesthetic and polyneuritic leprosy is that of Indian leprologists. The author leans very heavily on his sources, and seems to derive most of his knowledge from authorities rather than from critical personal observations and wide experience.

As an interesting and readable introduction to the subject, this little book may have some value, though the price for 120 pages of text (including diagrams and well-produced photographs) would seem rather high to those who might be expected to need it most and to benefit most from perusal of its pages.

The best chapters in the book are those dealing with clinical aspects of leprosy, the photographs of typical lesions being very good and helpful. One may well wonder, however, if in a shortish chapter on differential diagnosis, a page and a half devoted to such a rare condition as diastematomyelia is not somewhat disproportionate. In a monograph intended for the general practitioner faced with the problems of management of the patient with severe lepromatous leprosy, in reaction or not, a more practical and detailed approach would certainly be advisable and appreciated, both by the medical attendant and the patient.

Although the time-lag between preparation of the manuscript and publication may be offered as an extenuating explanation, it is disappointing not to find references to recent work on experimental transmission of Myco. leprae, and to read an uncritical repetition of investigations now somewhat dated. The eye would be helped by better proof-reading, an adherence to convention in italicization, and a conformity to established scientific usage in the matter of textual references.

Abstracts

The following 4 abstracts are reprinted, with permission, from *Trop. Dis. Bull.*, 1968, **65**, 8:

1. Tissue reactivity to tuberculin and ink in lepromatous leprosy with respect to the 'isopathic phenomenon', by P. KANAAR. Derm. Int., 1967, 6, 11.

The tissue reaction of leprosy patients to injected materials (tuberculin, leishmanin, milk, peptone, BCG or Indian ink) has been stated to resemble the histology of the leprosy lesions of the patient, regardless of his classification (see for example *Trop. Dis. Bull.*, 1955, **52**, 785; 1964, **61**, 795). This "isopathic phenomenon" would imply that the anergy of lepromatous leprosy is non-specific. However, some workers have failed to confirm these observations.

The present author failed to obtain any evidence in support of the isopathic phenomenon. Tuberculin and Indian ink were injected into apparently normal skin areas in 7 volunteer patients with treated lepromatous leprosy. Serial biopsies were made at intervals of 8 hours to 12 weeks, with fixation in Zenker's fluid. There were no more foam cells at the injection sites than at control sites in the same patient, and the irregular fluctuation with time of the number of foamy cells suggested that they were not associated with the response to the injected material. The foam cells were due to small randomly sited pre-existent lepromatous foci. All the other histological features were compatible with a normal reaction to tuberculin or ink. Further studies on 14 additional patients also gave negative results.

D. S. Ridley.

2. Thalidomide therapy in the lepra reaction, by J. CONVIT, J. M. SOTO and J. SHESKIN. Int. J. Lepr., 1967, 35, 446.

In this trial carried out in Venezuela, 24 patients (16 men and 8 women) were selected to test the efficacy of thalidomide in suppressing lepra reaction. Those not previously treated with corticosteroid were given 400 mgm./day, in divided doses orally, and fever settled in 48 hours; all symptoms disappeared within 4-5 days. There was one failure. Those previously treated with corticosteroid were given 500 mgm./day, steroid being suspended at the start of the trial; there was marked aggravation of the reactional state during the first 48 hours, regressing during the next 7 days and disappearing after 12-14 days. In both groups dosage of thalidomide was gradually reduced to a maintenance dose of 50 mgm./day. The authors state that patients previously intolerant of dapsone (DDS) were able to resume therapy while taking thalidomide, but no details are given. The only side-effects were constipation (at

higher dosage) and temporary oedema of hands and feet.

[The abstracter wishes to criticize two aspects of this trial. Firstly, it would have been preferable if 12 of the 24 patients had acted as a control group and had been given a tranquillizer such as chlorpromazine (Largactil) 25 mgm. 4 times a day instead of thalidomide. Secondly, he feels compelled to protest most strongly against the inclusion of women. Although the authors say that these women "had been submitted to special control to eliminate all suspicion of pregnancy", mistakes could have been made. Furthermore, this trial will encourage clinicians in other parts of the world to include women in their trials of thalidomide and disastrous results are foreseeable.]

W. H. Jopling.

 Tratamento experimental da lepra com Ro-4-4393 (Experimental treatment of leprosy with sulphormethoxine), by S. F. TARLÉ. Publções Cent. Estud. Leprol., 1967, 7, 2, 12.

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

"In anti-leprosy therapeutic the author uses a new sulfa of prolonged action, Ro-4-4393 (Fanasil— 'Roche'), in a group of 6 lepromatous patients, in the doses of 1.5 gr. to 2.0 gr. per week (single dose). The recession of the bacilloscopic indices was noted in practically all the patients, the action of the drug being comparable with that of sulfona, but showing as important facts almost an absence of side effects and acute manifestations, besides the convenience offered to the patient of a single weekly dose. One patient who had shown an aggravation of heart insufficiency owing to the use of sulfona, when submitted to our treatment showed excellent general health with no heart insufficiency."

 La Kelfizina nella terapia della lepra (Kelfizina in the treatment of leprosy), by A. A. BACCAREDDA-BOY, R. BERTAMINO and G. FARRIS. Derm. Int., 1967, 6, 109. English summary (5 lines).

Ten patients suffering from the leprotic form of leprosy were treated with Kelfizina (sulphalene) in the dermatology clinic at Genoa, Italy. Two were recent cases and had not had any other specific treatment; 4 other patients could not tolerate any specific treatment because of the violent leprotic reactions they experienced [3 of these had previously been given steroids]; one patient showed a recurrence of the disease 2 years after suspension of treatment by azosulphone and the remaining 3 had shown very little response to combined cycloserine+azosulphone treatment.

The dosage of Kelfizina was as follows: a single oral dose of 1 gm. the first week, 1.5 gm. the second week (1.0 gm. on the first day, and 0.5 gm. the second day) increasing by 0.5 gm. to 2.5 gm. till the total dose amounted to 62 gm. Laboratory and clinical examinations on blood and urine were done every 15 days and bacterial examinations of the nasal mucus and of films from the skin of the ear lobes and from 5 other sites were carried out. Three patients showed no reactions; 4 had mild leprotic reactions for 5-14 days which disappeared in 10-25 days while treatment continued; 3 patients showed severe leprotic reactions and in one of these patients treatment had to be suspended. [Before admission to the authors' clinic, this patient had been treated by steroids under the diagnosis of polymorphous bullous erythema.]

With regard to side-effects, although all patients showed some alteration in liver function before treatment started, no effects on the gastrointestinal tract, blood, liver or kidneys were noted and one patient already had a duodenal ulcer. In 5 patients the nodules and infiltration regressed, 3 improved slightly, one was unchanged. In 6 out of 8 the nasal mucus became negative and the Bacterial Index in the skin showed a definite reduction with an increase in the numbers of abnormal bacilli and of those with granules.

The authors conclude that Kelfizina has a definite effect on leprosy and is well tolerated, but it also has a tendency to provoke leprotic reactions which may be either slight or severe. These reactions, however, will disappear if treatment is continued but it is considered that a longer period of observation is advisable.

W. K. Dunscombe.

The following 2 abstracts are reprinted, with permission, from *Trop. Dis. Bull.*, 1968, **65**, 9:

5. Leprosy and genetics. A review of past research with remarks concerning future investigations, by B. BEIGUELMAN. Bull. Wld Hlth Org., 1967, 37, 46.

This paper, which should be studied in the original, summarizes critically and very competently recent investigations into various aspects of the possible genetic basis of leprosy.

Attempts have been made, without success, to correlate susceptibility to leprosy with such genetic markers as taste sensitivity to phenylthiourea, ABO and Rhblood groups, glucose-6-phosphate dehydrogenase deficiency, haptoglobins, transferrins, Au(1) antigen. Discrepancies in published results are attributable to such sources as imprecise data, bias, small series, selected populations, and deficiencies in technique. Pedigree analyses of families that include those suffering from leprosy have so far contributed little to knowledge of susceptibility and resistance to leprosy. Studies of the familial distribution of the late lepromin (Mitsuda) reaction are discussed in some detail because of their bearing on the possibility that transmission of the specific dimorphism of macrophages in respect of Mycobacterium leprae (presence or absence of ability to lyse) may be hereditary.

Geneticists interested in leprosy have concentrated on the investigation of inherited qualities that may be related to susceptibility to the disease, but the practical usefulness of any such correlations-even if established —is doubtful. The author indicates the vast lacunae in our knowledge of such fundamental matters as the significance of the late lepromin reaction in man, which is the only trait completely associated with leprosy, and suggests a research programme through which geneticists might contribute towards a better understanding of this reaction and its bearing on transmissible susceptibility to leprosy infection. By employing the experimental techniques of blood monocyte culture and observing the transformation of these cells into macrophages possessing or not possessing the ability to lyse living Myco. leprae, the author considers that real progress may be achieved.

S. G. Browne.

Syndromes paraplégiques en milieu lépreux. A propos de 12 cas observés en Nouvelle-Calédonie (Paraplegic syndromes in a leprous environment), by G. DESMOULINS and G. ZELDINE. Bull. Soc. Path. Exot., 1967, 60, 482.

Among 721 patients of Melanesian race suffering from leprosy in New Caledonia the authors have found 12 with spastic paraplegia of obscure origin, whose case histories they give; there were also another 4 possible cases. This trouble was not found among 158 non-Melanesian patients with leprosy. Among the general population the disease is rare and when found has obvious causes.

The only common factors were Melanesian race, leprosy of any type, and treatment for some years with sulphones. Investigations showed no evidence of compression of the cord, and no definite evidence of infection. Although some of the patients showed serological changes of treponematosis, these were probably due to yaws rather than syphilis. No evidence could be obtained of viral or rickettsial infection. Spinal fluid showed no notable changes, and the raised serum globulin levels occur in all leprosy patients

The authors speculate on possible plant poisons, and on the relationship to kuru. [They do not mention the similar condition, occurring in Africa though not essentially in persons with leprosy, which may be related to aneurine deficiency.]

A. C. E. Cole.

The following 5 abstracts are reprinted, with permission, from *Trop. Dis. Bull.*, 1968, **65**, 10:

7. Gynécomastie du lépreux et obstacle au flux lymphatique spermatique (Testicular lymphatic obstruction in gynaecomastia in leprosy), by A. CARAYON, J. LANGUILLON and G. FOUCHER. Bull. Soc. Méd. Afr. Noire Lang. Fr., 1967, 12, 552.

Lepromatous leprosy is probably the commonest cause of gynaecomastia, yet the undoubted association of testicular damage in leprosy with gynaecomastia is neither as clearly documented nor as lucidly explained as it should be. Although some testicular damage is clinically demonstrable in perhaps 30% of (male) patients with established lepromatous leprosy and is histologically apparent in 90%, gynaecomastia was present in only 8% of 250 leprosy patients in the authors' series. [Radiographic examination of the male breast is considered to be a useful procedure for the detection of early subclinical damage.]

In patients with lepromatous leprosy, in whom gynaecomastia was present, histological examination of testicular tissue revealed some hyperplasia and vacuolization of the Leydig cells (which was not due to direct action of *Mycobacterium leprae*), with some significant extracellular ordema. The authors' new and important finding was fibrosis of the testicular lymphatics, with consequent constriction of the lumen of the vessels. Other examinations (e.g., various biochemical determinations, liver function tests, and so forth) and the nutritional state were not considered to be sufficiently abnormal to account for the occurrence of gynaecomastia. By means of lymphography of the testicular and funicular lymphatic vessels, the authors were able to show stasis and back-flow of lymph and blocking either of the spermatic and lymphatic vessels themselves or at the lymphatic node of Horowitz-Zeissl.

The appearance of gynaecomastia would, according to the authors, seem to depend on a concatenation of more than one factor: *viz.*, direct damage of the testes by lepromatous leprosy (as shown by dysfunction of the damaged Leydig cells) and a mechanical lymphatic statis due to fibrosis of the deep lymphatic nodes following leprotic infiltration.

[Further work is required to substantiate this interesting hypothesis, accompanied by more convincing radiographs.]

S. G. Browne.

Effects of DDS on lysosomal enzymes from leprosy tissues, by A. G. PALEKAR and N. G. MAGAR. Int. J. Lepr., 1967, 35, 436.

The authors have studied the specific activities of acid phosphatase, cathepsin, ribonuclease and aryl sulphatases from lysosomes of tissues of normal subjects and of leprosy patients:—(i) who had not been treated with dapsone (DDS); (ii) who were being treated with DDS; and (iii) who had undergone DDS treatment for 6-10 years but who were bacteriologically negative for *Mycobacterium leprae*. The examinations were made on 250-300 mgm. of tissue obtained by biopsy from the arms of normal persons and from the lesions on the arms of patients with lepromatous, tuberculoid and maculoanaesthetic types of leprosy.

The results of the examination, the methods of which are given as references, are presented in tabular and graphical form. The lysosomal fraction and the tissues of leprosy patients of all types who had not undergone DDS treatment, showed a significant high activity for all 4 enzymes when compared with the same fraction of normal tissues. In contrast the lysosomal fraction from the tissues of leprosy patients who had undergone DDS treatment for 6-10 years and who were bacteriologically negative, had almost normal activities and the activities of the fractions from tissues of the patients who were undergoing DDS treatment were intermediate. The results therefore indicate that the increased specific activities of lysosomal enzymes from the tissues of leprosy patients of all types decreased significantly with effective DDS treatment.

The authors consider their results suggest that the biochemical evidence could be integrated in an understanding of the general physiology of the cell as an effective device allowing the cell to utilize organic matter incorporated after the DDS treatment. The DDS may be acting principally on the lysosomal component, increasing its hydrolase activity, altering cell metabolism in some way and rendering the cell cytoplasm unsuitable for multiplication and survival of the bacillus.

S. R. M. Bushby.

9. Acute dapsone poisoning, by R. S. RAJAGOPALAN and J. RAMA RAO. J. Ind. Med. Ass., 1967, 49, 439.

A woman aged 20 years swallowed 375 mgm. dapsone (provided for her husband, who had leprosy), at 9 p.m. Next morning she was found to be sweating and vomiting profusely and was taken to hospital. She was conscious and complained of severe nausea and giddiness. Respiratory rate was 26/minute; pulse rate 150/minute. The tongue and tips of the fingers were bluish. A sample of blood was greyish black and contained much methaemoglobin on spectroscopic examination. The urine was normal. She was given $1~{\rm pint}$ of 5% glucose by intravenous drip, as corbic acid 500 mgm. 6-hourly and ethylbutamide and propylbutamide 2 cc. intravenously 6-hourly. Cyanosis increased and she became restless. 100 cc. of 12.5% mannitol was given by intravenous drip. Methylene blue (50 mgm. capsule) was given every 6 hours but she vomited. She gradually improved in 48 hours and began to pass urine. On the fourth day, the blood appeared free from methaemoglobin but tachycardia persisted for 2 weeks. The ascorbic acid and methylene blue were given in order to reduce methaemoglobin to haemoglobin.

F. Hawking.

A kinetic method for the study of activity of drugs against Mycobacterium leprae in mice, by C. C. SHEPARD. Int. J. Lepr., 1967, 35, 429.

Most studies of the activity of drugs against Myco-bacterium leprae in mice have followed the procedure in which administration of the drugs starts on the day of infection and is continued till termination of the experiments. Thus, only inhibition of multiplication was usually observed and the killing of Myco. leprae by the drug was not measured. In an earlier paper [Trop. Dis. Bull., 1967, 64, 1212), the author reported attempts to measure the bactericidal activity of dapsone (DDS) by allowing the Myco. leprae to multiply

to above 10^6 organisms per mouse before starting the drug, and then at intervals counting the bacilli. This procedure was very laborious and in the present paper he describes a kinetic method that takes advantage of the accuracy available in the logarithmic phase of the growth curve of *Myco. leprae.* The drug is given for only a limited period early in the growth curve and its effect is measured by the subsequent delay in appearance of the logarithmic phase of growth.

The growth curve in control mice was monitored from pools of 4 mice, killed at monthly intervals, starting 3 months after inoculation. Soon after the bacterial population had increased to the normal plateau levels above 10⁶, counts were made on similar pools of 4 mice from each of the treated and control groups, and the counts were repeated after intervals of 3 months. The drugs examined in the diet were DDS, ranging from 0.1% to $0.00001\,\%$, isoniazid 0.01% , 4,4'-diacetyl-diaminodiphenylsulphone (DADDS), thiambutosine (diphenylthiourea, DPT) and *p*-aminosalicylic acid (PAS); streptomycin, 2 mgm. thrice weekly, was injected. Some of the drugs were given in combination. In interpreting the results, 2 simplifying assumptions were made: (i) that after the beginning of administration of an effective drug the cessation of bacillary growth is rapid enough to prevent significant increase in numbers of bacilli, and (ii) that as soon as the inhibitory drug disappears from the tissues, bacillary growth begins at the rate observed in the control.

The results are given in tabular and in graphical form and they show that none of the treatments eradicated the infection. Streptomycin 2 mgm. thrice weekly and 0.1% DPT in the diet were each bacteriostatic. Isoniazid 0.01% and PAS 0.6% in the diet were each inactive. DDS 0.01% in the diet was bacteriostatic and probably partially bactericidal, the killing rate being estimated not to exceed 77-84%; 0.1% in the diet was no more effective. The combination of 0.01% DDS with either streptomycin or DPT was no more effective than DDS alone and isoniazid appeared to antagonize the antibacterial effect of DDS.

S. R. M. Bushby.

Improved method for observing elongation of Mycobacterium lepraemurium in vitro, by M. NAKAMURA. Int. J. Lepr., 1967, 35, 505.

Elongation in vitro of Mycobacterium lepraemurium was described by HART (Int. J. Lepr., 1965, **33**, 504) and by HART and VALENTINE [Trop. Dis. Bull., 1964, **61**, 51) and it is a possible guide to the complete cultivation of this organism, but the method used by Hart and Valentine involved the risk of damage through centrifugation and washing for removal of the high concentrations of sucrose in the medium used for culture. The slide culture method is used in the present experiments.

Smears are prepared from lepromas which have been homogenized in sterile water and suspended in 0.1%bovine albumin V fraction. After being dried at room temperature the slide is immediately placed in the medium described by Hart and Valentine, but with slight modification, and incubated at 37° C for periods up to 30 days. A slide is fixed immediately after drying to serve as a sample of the initial inoculum. For fixation, the slide is transferred to 10% formalin water; it is then well washed and stained by Ziehl-Neelsen's method. For assay of elongation, photographs are made of the slides to give a final magnification of 1,000.

In this method, elongation was observed at pH 6.0, but not at pH 8.0. Infectivity activity of the bacilli was parallel to grades of elongation for 15 days after incubation, as judged by the ability of a 10% lepromatous suspension to produce lepromas in mice after incubation under the same conditions as the slide. However, after incubation for 30 days at pH 8.0, but not at pH 6.0, infectivity was still maintained, even though no elongation occurred at this pH value. Hart and Valentine observed that elongation gradually continued for about 2 months after incubation, but in view of the loss in infectivity it is doubtful whether elongation after incubation for this period represents a vital process.

Further studies on factors affecting the elongation phenomenon observed by this method are now in progress.

S. R. M. Bushby.

OBITUARY Cyril I. Crowther

The Leonard Wood Memorial in particular, and leprosy workers throughout the world, mourn the loss of a most distinguished layman who for 8 years was President of the Memorial. He died on 27 October, 1968, at the age of 73. It was during his term as President that the Memorial founded leprosy research units at John Hopkins University (Baltimore), in Washington, D.C. (including studies by electron microscopy), and in Cebu, Philippines. Cyril Crowther was the genial and gracious stimulator of these and other projects. Ever mindful of the need for training young scientists in leprosy research, he encouraged the Memorial to develop its programme in this field. We salute a real friend of leprosy and leprosy workers, and express to his widow, his children and grandchildren our sincere condolences.
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