LEPROSY REVIEW

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CONTENTS

Edited by DR. J. ROSS INNES, Medical Secretary of the British Leprosy Relief Association, 8 Portman Street, London, W.1, to whom all communications should be sent. The Association does not accept any responsibility for views expressed by writers.

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EDITORIAL

Visit to India

A. *The All India Leprosy Conference, December* 1959, *Bombay*

The 7th Conference of the All India Leprosy Workers and the 4th of the Indian Association of Leprologists was a joint affair, held in Bombay, 14th—18th December 1959. This highly successful Conference had as Chief Patron Shri Sri Prakasa, Governor of Bombay, and as Patrons Shri Y. B. Chavan, Chief Minister, and Dr. Jivraj N. Mehta, Minister of Finance, and as Chairman of the Executive Committee Shri N. K. Tirpude, Minister for Social Welfare. The Secretary was Dr. T. B. Patel, and Joint Honorary Secretaries Dr. P. Kapoor and Dr. J. N. Vazifdar. Two publications for the Conference were issued by Hind Kusht Nivaran Sangh (Indian Leprosy Relief Association). These were the "Programme", which contained summaries of the 29 papers delivered at the Conference, and "Souvenir" which contained 100 pages and 76 illustrations, chiefly made up of the following articles:—

All India Leprosy Workers' Conferences	T. N. JAGADISAN
Indian Association of Leprologists, Its Origin and Development	K. R. CHATTERJEE
Government of India and Leprosy Control	Y. K. SUBRAHMANYAM
Leprosy Control Work in Bombay State	T. B. PATEL and P. KAPOOR
Pathology of Early Lesions in Leprosy	V. R. KHANOLKAR
The Diagnosis of Leprosy and its Difficulties	S. N. CHATTERJEE
The Leprosy Patient and his Treatment	E. MUIR
The Present Concept of the Role of Isolation in the Control of Leprosy	N. FIGUEREDO
Diet for Leprosy Patients	M. V. RADHAKRISHNA RAO and M. S. KOTNIS
The Role of Physiotherapy in Leprosy	PAUL W. BRAND
Rehabilitation of Leprosy Patients	M. D. AMTE
Difficulties in the Rehabilitation of Leprosy Patients	M. DIWAN
Leprosy and Law	P. SEN
Bibliography of Publications on Leprosy from India	N. MUKERJEE

The Editor was present throughout at the actual Conferences and enjoyed them and the discussions very much. The best way to give readers an idea of the interesting fare offered would be to give our own summaries of the papers delivered.

1. DR. S. N. CHATTERJEE dealt very fully and helpfully with *The Diagnosis of Leprosy and its Difficulties*. His paper in full text, with 62 illustrations, is available in the Souvenir, p. 38. He began with skin conditions simulating leprosy, from leucoderma to occupational dermatitis, and dealt with dermal leishmaniasis, neurofibroma, many nerve conditions both primary and secondary, vascular conditions, and gave wise advice about the assessment of thickened nerves, and bacilli in smears, and a warning that leprosy is sometimes missed owing to some complication, e.g. a change in a leprotic lesion which causes it to be mistaken for erysipelas or cellulitis. From experience in Africa, about the only thing we might add to Dr. Chatterjee's big list is onchocerciasis.

2. DR. DHARMENDRA read a paper on the *Classification of Leprosy*. He described the position reached at the Tokyo Congress, 1958. The maculo-anaesthetic group favoured by Indian leprologists does not seem acceptable to the Hispano-American and Luso-American workers, and the Tokyo Congress made no recommendation on this point. Indian leprologists want polyneuritic lesions to be placed in a separate group, in the sense of periphero-neuritic. Dr. Dharmendra comments that though it has been agreed that the basis of primary classification of leprosy should be clinical, the stress always tends to be placed on histopathology.

3. DR. N. FIGUEREDO also read a paper on the *Classification of Leprosy*. From his studies using Dharmendra antigen and bacteriological examinations on patients and contacts he recognises leprosy in the following stages: infected or silent phase, primary lesions, pre-nonlepromatous macules, minor or major tuberculoid, maculo-anaesthetic, indeterminate, reactional tuberculoid, borderline, primary or pure polyneuritic, prelepromatous macules, and lepromatous. The progress of all lesions tends either towards the polyneuritic or the lepromatous. The indeterminate also tends this way or to the lepromatous through the reactional tuberculoid and borderline phases. Transition from the maculo-anaesthetic to the minor or major tuberculoid has not been observed, nor the reverse. Minor and major tuberculoid and the maculo-anaesthetic tend only towards the polyneuritic. He recommends the inclusion of reactional tuberculoid in the intermediate group, and applying "borderline" to lesions on the verge of progression to lepromatous.

4. DR. J. ROSS INNES of London read a paper on *Mercaptan Compounds in Leprosy and Tuberculosis*. G. W. DRIVER and G. E. DAVIES contributed to this paper a valuable survey of the literature on the mercaptan compounds. The clinical study of these hopeful compounds began in 1950 by Del Pianto who tried sodium ethyl sulphate against animal and human tuberculosis and in 1958 reported at the 7th International Congress of Leprology that he had had good results against leprosy. Other workers studied ethyl mercaptans, and

in 1956 Davies and Driver and others of ICI Research Laboratories reported on the study of 200 mercaptan and related compounds in mice tuberculosis and selected diethyl dithiol*iso*phthalate as the most active. They also found it to be effective by inunction. Davey and others have reported on its action in human leprosy and the results so far suggest an unusually rapid bacteriocidal effect. Drug resistance develops at about the fourth or fifth month when the ICI product Etisul is used alone, but Davey has latterly found that the use of DDS and DPT by mouth from the beginning of the trial delays indefinitely the onset of drug resistance and the total effect is a reduction in the bacterial index greater and faster than anything known before. There is a strong case for wider clinical trials against leprosy of this very interesting drug. At the present time, trials are in progress against human tuberculosis with equally hopeful results. It is not likely that it will be an expensive drug when finally it arrives on the market.

5. DRS. N. MUKERJEE and P. GHOSAL described *Recent Developments in the Chemotherapy of Leprosy*, discussing depot injections of DDS, newer sulphone derivatives, new drugs and antibiotics and they called for more trials on many of them, both alone or in combination, for any therapy which is more effective than DDS will be welcome. For parenteral action they consider the best is a depot suspension of microcrystalline DDS in 0.2% sodium carboxy methyl cellulose in normal saline. They found DDSO as effective as DDS. DPT is as effective as DDS and a useful alternative drug under certain circumstances. Further trial with Etisul is necessary, also the benzaldehyde derivative of INH. Combination of DDS with either INH, DPT, or Etisul, seems to produce a little better effect than DDS alone.

6. DR. A. T. ROY read a paper on the *Treatment of Leprosy with SU 1906* (*DPT*). He tried SU 1906 or 4-butoxy-4 dimethyl-aminodiphenylthiourea in 5 lepromatous, 1 major tuberculoid, which was bacterially positive, and 1 minor tuberculoid (this was a child aet. 4 years). The children in the series were given dosage of 0.5 to 1.5 g. daily. The adults were given 1 to 3 g. These doses were well tolerated and clinical improvement was noted. The adult doses were then tried on the children and were well tolerated. The lepromatous cases had their dosage gradually increased, and all took 4.5 g. without any toxic signs or reaction. One of the lepromatous cases began to show signs of reaction when 5 g. dose was given, but none of the 7 cases showed any sign of reaction with the recommended dose of 1 to 3 g. A progressive reacting case was now included in the series, who was intolerant to sulphone of any type. He has done well on 2.5 g. without reaction, and with rapid clinical improvement.

The bacillary index was influenced, with results much the same as Davey found in his cases, though with ups and downs.

7. DRS. J. E. SOMERSET, N. MUKERJEE and N. R. SEN dealt with

Lagophthalmos in Leprosy: Its Surgical Treatment. Complete or incomplete defect of closure of the eyelids is common in leprosy, often accompanied by ectropion of the lower lid. This leads to exposure keratitis and its complications. The more common operation available is lateral tarsorrhaphy, but Axenfeld's operation is preferable in some cases. This consists of the insertion of a silk suture under the skin of the upper and lower lids and under the lateral and medial tarsal ligaments. The size of the palpebral fissure can thus be adjusted to its optimum by tightening the suture. The stitch is left in position for several months until its track has become fibrous. The removal of the stitch thus leaves a fibrous band which takes over its action. The authors used this operation in 6 cases with good success.

8. DR. N. H. ANTIA described the *Correction of Facial Deformity in Leprosy by Plastic Surgery.* Though large numbers of leprosy cases are now being cured, if the treatment has been started late there will be many left with disfigurements and deformities. Deformities of the hand and limbs will need surgical correction in order to help the patient to become a useful citizen, and disfigurements of the face by perpetuating the stigma attached to leprosy will hinder rehabilitation. The author therefore has taken special interest in the correction of facial deformities in the Kondhwa Leprosy Hospital. (*a*) The sunken nose is the most striking of these and he has found the operation of postnasal epithelial inlay, by supplying fresh lining through an intraoral operation, to be very satisfactory, even in advanced cases, and support can then be provided by a dental prosthesis or a bone graft. (*b*) Total destruction of the nose is best dealt with by a tube pedicle rhinoplasty. (*c*) Lagophthalmos or paralysis of the orbicularis muscle of the eye, which is common in leprosy and may lead to loss of sight, can be corrected by taking advantage of the fact that the adjacent temporalis muscle innervated by the 5th nerve is usually not affected. A fascial sling is made to encircle the palpebral fissure and attached to an innervated slip of the temporalis muscle. Its contraction closes the eye and corrects the deformity. This method is better than lateral tarsorrhaphy, which is apt to fail in part by recurrence of the trouble in the residual unclosed portion of the palpebral fissure. (*d*) Lost eyebrows can be replaced by grafting hair-bearing scalp as a free graft, or as a temporal artery pedicle flap. (*e*) A face lift can be given to correct the wrinkled appearance of premature ageing. (*f*) Elongated ear lobes can be trimmed, and thickened skin and nodules shaved down. (*g*) Perforation of the palate can be closed using a plastic procedure which sufficiently elongates the soft palate to produce normal speech. The author makes a plea for the opening of centres for plastic and reconstructive surgery and for training surgeons in this highly satisfactory field.

9. DR. R. H. THANGARAJ dealt with *Foot Ulceration in Leprosy.*

He wished to stress the distinction between the pathological and mechanical factors in the causation of ulcers of the feet and absorption of bones. Arterial changes may both lead to ulceration and result from it. The limitation of blood supply to an ulcer in leprosy is not due to vasoconstriction but to vasostrangulation by a mass of nonelastic fibrous tissue caused by previous ulceration. The first ulcer is due to an excessive amount of walking, a badly fitting shoe, or some slight injury. It can be healed, but as it heals creates fibrous tissue which in its turn predisposes to further ulceration. At the time of the first ulcer the patient will be much helped by hospitalization and education in the prevention and care of ulcers. The author lists causative mechanical factors; (*a*) excessive walking; (*b*) injuries from sharp stones, thorns, and nails in the shoes; (*c*) irregular weight bearing; (*d*) the concentration of weight at certain points of the foot; (*e*) the projection of bone downwards towards the sole of the foot causing localised pressure; (*f*) drop foot and inversion caused by paralysis. For the last mentioned the standard operation is to fix the tibialis posterior to the middle cuneiform bone with stainless steel wire. The author's modification is to pass the tibialis posterior through the interosseous space about 5 inches (12.7 cm.) above the ankle and then through the extensor digitorum longus and then into the tibialis anterior. A plaster below the knee is applied to maintain the foot in dorsiflexion, and the plaster is removed in 4 weeks. Physiotherapy is fully used.

10. DR. D. N. BOSE dealt with *Plaster Therapy with Physiotherapy in Deformities and Chronic Neurological Syndromes in Leprosy Patients*. He described simpler methods which can be used with success in default of skilled surgical personnel and equipment. The application of plaster rests and heals many deformities, and for the prevention of recurrence he gives physical exercises to the parts, regular massaging with oil, preferably hydnocarpus oil, and subcutaneous injections of Hydnocreol in doses of 3 to 4 ml. at least twice a month in the deformed parts and by the sides of the nerves.

11. DR. M. NISHIURA gave a paper on *Electron Microscopic Studies of Human Leprosy Lesions*. He has used metal-shadowing of ultra-thin sections of leprosy lesions to study the fibrous elements by electronmicroscopy (collagen, reticulin, and elastic fibres). In tuberculoid lesions many collagen fibrils are separated from each other or dissolved, but elastic fibres look normal and are easily recognised. In lepromatous lesions, collagen, reticulin, and elastic fibres are well preserved, though the elastic fibres are a little difficult to identify. The necrotic process in tuberculoid skin and nerve lesions was also studied. Intracytoplasmic coagulative necrosis was noted in tuberculoid skin lesions in a few isolated cells, but in nerve lesions it was found on a large scale, and the whole nerve trunk may be packed with necrotic masses.

12. DRS. M. NISHIURA, S. M. SIRSAT, and V. R. KHANOLKAR also reported on *Electronmicroscopic Study of Leprosy Lesions.* After metal-shadowing of ultra-thin sections from the skin and great auricular nerves the electronmicroscopic study showed that the collagen fibrils are not damaged in lepromatous lesions, but in tuberculoid they are often separated from each other or entirely absent. Elastic fibres are more easily found in tuberculoid than in lepromatous lesions, and they do not appear abnormal. A few isolated necrotic cells which show coagulative changes in the cytoplasm are found in tuberculoid skin lesions. The necrotic process in tuberculoid nerve lesions begins as a coagulation of the cytoplasm and the formation of myeloid bodies and droplets of lipid inside the cytoplasm of epithelioid cells. Destruction of the cell membrane of these necrotic epithelioid cells is followed by the release of various degenerated cell materials which form a caseation necrosis of the whole nerve trunk. The commonest form of the necrotic mass is a helicoidal thread at least 15 to 25μ in breadth. These threads mass together and may be found in an occasional necrotic cell of the skin and more widely in necrotic lesions of the peripheral nerves.

13. DR. V. R. KHANOLKAR has a paper on the *Pathology of Early Lesions in Leprosy*, which was published in the *Souvenir* of the Conference pp. 30–37 and is abstracted here and given for the sake of completeness. The paper has one schematic text-figure of the cellular elements inside the endoneurium and perineurium in relation to the descending nerve fibre in leprosy. There are also 13 illustrations of the histology of nerve fibres and cellular elements in leprosy, some of them electronmicrographs. About 12 years ago Dr. Khanolkar began a careful clinical and immunological examination and study of the histology of the skin, in early cases of leprosy and contacts. He later added a standardised lepromin test, and fluorescence microscopy for the fluid obtained from skin biopsies, newer techniques for studying the condition and structure of the peripheral nerve fibres, and finally electronmicroscopy for the finer structure of cell constituents and the intercellular material.

The group of contacts with leprosy comprised 138 adults and 24 children who were clinically free of leprosy. Of them the 24 children and 68 adults showed the presence of acid-fast bacilli in the skin, after application of a concentration technique to the skin biopsies. Later more adults became bacillus-positive and a high proportion of those who were lepromin-negative became lepromin-positive. Of the total group of 162 persons, 69 developed recognisable physical signs of early leprosy.

Contacts of tuberculoid and lepromatous leprosy were next studied separately. Clinically and bacterially positive leprosy developed in 27% of those in contact with the tuberculoid type and 39% in those in contact with the lepromatous. An arbitrary division

of leprosy patients into "open" and "closed" types therefore seems unjustifiable.

It is not possible to predict which of those contacts who show leprosy bacilli in their skin will develop leprosy and which will escape it, so this can be called the "silent phase". In the histology of this early stage there is nothing special, except for the occasional finding of a histiocyte with one or two intact or fragmented acid-fast bacilli in the cytoplasm. Sometimes the histiocytic cytoplasm takes a granular or diffuse basic stain which does not decolourise with weak acids. Khanolkar has found this only in the early stages of leprosy and calls such cells "fuchsinophil cells". In the next phase there is a non-specific type of cellular response; this is the indeterminate phase. Later the cell response becomes typical of lepromatous, dimorphous, or tuberculoid leprosy.

In the histology of all these three types the bacilli seem to prefer to be found in the axoplasm of the cutaneous nerves and there is an inflammatory response which tends to be located in areas of the dermis which are richly supplied with nerve filaments, such as hair follicles, sweat and sebaceous glands, and erector pili muscles. The sensory cutaneous and the sympathetic fibres seem to be affected early and greatly, and show the most of later damage in all forms of the disease.

In *lepromatous leprosy* the bacilli gain access to the axoplasm of the preterminal axons of regenerating fibres. The electronmicroscope shows bacilli lying interspersed with mitochondria. The bacilli seem to move towards the dorsal root ganglia and go no further. The axoplasm shows degenerative changes and looks worm-eaten in ultra-thin sections, and bacilli with a lipoid covering are seen lying in the section. The myelin sheath also undergoes progressive degeneration. At intervals along the nerve fibre there are clumps of great multiplication of bacilli, which probably burst out in the endoneural and perineural spaces. Contemporaneous with the degenerative changes regenerating nerve fibres migrate along the collapsed Schwann tubes from the adjacent unaffected nerve fibres, and the Schwann cells convert into ribbonlike bands called "Büngner's Cords". The bacilli seem to be able to remain a long time in the Schwann cell cytoplasm unharmed. The bacilli which escape out of the nerve fibres are taken up by the endoneural cells and histiocytes, which pack closely into a sheath of lepra cells round the nerve fibres. The pressure of packed lepra cells and resulting ischaemia seems to be the main cause of disturbance in structure and function of the nerves.

In the dermis the early change in lepromatous leprosy is the appearance of collections of chronic inflammatory cells in strands or groups around nerve twigs and plexuses. The grouped cells form a richly vascular granulation tissue on a reticulum of very fine fibres.

Most of the cells are histiocytes. In their cytoplasm the bacteria multiply and quickly come to be surrounded by a lipoid envelope which under the electron microscope appears as an opaque droplet. In this droplet clear zones appear which adjoin the bacteria. These clear zones fuse with the adjoining coverings of multiplying bacteria, and finally the whole cytoplasm appears foamy (the Virchow or Lepra Cell). The dermis in later stages of leprosy has large areas forming a continuous sheet of chronic inflammatory tissue with huge numbers of bacilli, and with lepra, mononuclear, and plasma cells.

In the dermis the early change in *tuberculoid leprosy* is the invasion by foci of mononuclear cells and histiocytes, usually located along the channels occupied by the neurovascular bundles. The histiocytes transform into epithelioid cells and occasional giant cells round a core of fine nerve twigs. By electronmicroscopy of ultra-thin sections the cytoplasm of epithelioid cells is seen to contain a smooth reticulum and diffuse lipoid dust, and mitochondria increase greatly during the active and reactive phases of tuberculoid leprosy. The epithelioid cells rapidly engulf and destroy leprosy bacilli and other tissues such as collagen and nerve fibres which are in their area. The nerve fibre changes are characteristic; beginning with Wallerian degeneration they go on to necrosis. Throughout all stages there is a continuous attempt at regeneration of nerve fibres in adjacent unaffected areas of skin, consisting of a sprouting of fine neurofibrils.

In *dimorphous leprosy* the lesion shows mixed characters in the same or different lesions of the same subject, and is an intermediate response to the infection.

Khanolkar comments on the above findings. The leprosy infection is probably transmitted by skin contact, by repeated or even single contacts of the bare skin of a susceptible person with the skin of a lepromatous case, and even also dimorphous and reacting tuberculoid cases. It appears that the bacilli must reach the external surface of the body in sufficient numbers. Even after they survive in the host and grow in his tissues they may not produce the disease. It seems that they must multiply rapidly and have a certain degree of biological activity so that the responses and reactions of the host become recognisable as clinical leprosy. It is still not known how the leprosy bacilli introduce themselves into the axoplasm of nerve fibres in the skin. NISHIURA thinks that it starts with the regenerating axon, whose terminal expansion actively phagocytises free-floating bacilli in the tissue fluids of the skin. The problem of the persistence of leprosy bacilli in the body for long periods of time, even after a long course of therapy, is probably due to their lodgement in Schwann cells, and the rapid multiplying and freeing of the bacilli in tissues outside the nerves must be influenced by general body conditions, such as puberty, pregnancy, intercurrent diseases, and unsuitable treatments.

We still do not understand the factor or factors which determine the change of a histiocyte into an epithelioid or a Virchow cell. For the last 2 years KHANOLKAR has cultivated an acid-fast mycobacterium identical with *M. leprae* from 4 different cases of leprosy and kept it growing in artificial media. BINFORD and CHATTERJEE have reported experiments in laboratory animals which begin to throw light on transmission. KHANOLKAR has found some promise in similar experiments on mice.

14. DRS. A. PAUL JAYRAJ and D. CHOWDHURY gave their papers on *Epithelial and Subepithelial Innervation in Lepromatous Leprosy.* They applied the silver impregnation method to biopsy material from the skin of 20 advanced lepromatous cases, and found intact nerve fibres in the epidermal and subepidermal layer of lepromatous skin. It is not known whether these fibres are carrying impulses or not.

15. DR. R. G. COCHRANE read a paper on *Immunity in Leprosy.* He pointed out the difficulty of this subject. The strength of the lymphocytic response may be a measure of immunity in leprosy, and it may be used to assess the action of the lepromin test and of BCG vaccination. One injection of BCG may not produce an effective immunity and perhaps it will need to be given repeatedly. Further it is by no means certain whether the immune response, as indicated by the appearance of tissue allergy, is determined by the type of the disease or whether the allergic response determines the type of disease.

The lepromin reaction is usually regarded as merely an indication of the stage of immunity in the tissues. Dr. Cochrane expounded the concept of a conflict between the bacillus and the tissues, on the outcome of which either lepromatous or tuberculoid leprosy emerges. Thus established, tuberculoid leprosy is that form of the disease in which the tissues finally gain the upper hand. His concept of dimorphous leprosy relates the clinical and histological signs of leprosy to the individual immunity state. He thinks that erythema nodosum leprosum is a bacterial allergy and is produced when the bacilli are undergoing great changes in morphology, and that progressive lepra reaction has no direct bearing on immunity but is simply a biochemical reaction to circulating antibodies, as is indicated by the mobilization of plasma cells and the marked reversal of the serum globulin/albumin ratio in the blood.

16. DRS. B. M. BRAGANÇA and K. PRABHAKARAN reported on their studies of *Some Aspects of the Metabolism of M. Leprae.* They wished to explore the enzyme metabolism of *M. leprae* obtained from lepromatous nodules, first separating the bacilli from the nodular tissue by a method which did not inactivate the enzymes. They used differential centrifugizing and used aqueous solvents known not to denature proteins and enzymes. The final fractions were

found free of tissue debris. The separated organisms were subjected to metabolic studies of two kinds, one the nature of the enzyme pattern by which the bacilli metabolise various substances to obtain the required energy, the other the nature of the enzymes involved in the metabolism of amino-acids. It was found that human leprosy bacilli contain several of the oxidative enzymes, namely cytochrome oxidase, succinic oxidase, cytochrome reductase, lactic dehydrogenase linked to DPN, and pyruvic oxidising enzymes. In general these indicate that the bacilli can obtain energy for cellular activity by the aerobic oxidation of nutrients such as glucose, lactate, and pyruvate. Unless the bacilli were crushed the aerobic metabolism could not be significantly demonstrated *in vitro*. This indicates that the lipoidal capsule around the mycobacteria may affect the accessibility of the various substrates tested to the enzyme centres in the cell. As regards amino-acid metabolism the work is at an early stage but it was found that both glutamic acid and tyrosine are actively metabolised by the separated organisms.

17. DR. K. YANAGISAWA of Japan reported on his *Studies on the Potency Test of Dharmendra Antigen*. The potency of lepromin has previously been assayed mainly by the enumeration of leprosy bacilli of the antigen. However by analogy with similar studies on tuberculin and BCG reactions it seemed worthwhile estimating the potency of Dharmendra antigen by the grade of reaction itself rather than by enumeration of the bacilli. He carried out experiments on 3 lines (*a*) Leprosy bacilli obtained by trypsinizing human lepromas were applied to sensitize guinea pigs: (*b*) potency of different samples of Dharmendra antigen was compared in guinea pigs sensitized with leprosy and tubercle bacilli: (*c*) potency of different samples of Dharmendra antigen was compared as between leprosy patients and guinea pigs sensitized with tubercle bacilli. The results all tended to show that assay of potency of Dharmendra antigen can be performed with guinea pigs sensitized to tubercle bacilli.

18. DRS. B. B. GOKHALE and B. B. DESAI gave a paper on *Cholinesterase Activity in Leprosy*. The physiological function of this enzyme in the blood stream is not yet clearly understood. It is possible that it is a mere barrier to destroy any acetylcholine which leaks out into the blood stream; but it is located in high concentration in the neuronal surface and its main function is to hydrolyse acetylcholine which is directly associated with the nerve action potential. This hydrolysis of acetylcholine is necessary for the return of the nerve to normal, and any condition that reduces or inhibits it will delay the return of the nerve to normal. The organic phosphorus insecticides have been found to inhibit cholinesterase by about 80% in some cases and typical neurological symptoms resulted in such cases. Therefore it was thought worthwhile to study the enzymatic activity of serum samples in normal cases and leprosy cases, and a

statistically significant lowering of the activity was observed in the leprosy patients. This now provides a basis for a planned study in comparable groups of leprosy in various stages.

19. DR. Y. K. SUBRAHMANYAM described the *Draft Scheme for the Third Five-Year Plan on Leprosy*. It is estimated that there are about 2 million cases of leprosy in India, which is a moderate estimate. Working on the basis of this estimate and on an incidence of 20 per thousand in endemic areas (the incidence varies from 10 to 60 per thousand) the population to be covered would be 100 millions. So far the Government of India has established 72 units and aims at a target of 100 units by the end of the 2nd Five-Year Plan now in progress. In the Third Plan period a further 150 new control units would be needed to achieve full coverage. Two Rehabilitation Centres are planned, one in the southern and one in the northern zone, for each of which more detailed planning is required, and for each of which a sum of Rs. 25 lakhs (£187,500) is expected to be needed. Training centres are very important and these will be provided by the State Governments, with a probable subsidy from the Central Government. About 4,600 paramedical and 1,900 social workers will be needed to be trained in the Third Plan Period. An All-India Training Centre in Physiotherapy and Orthopaedic Surgery is being discussed, in consultation with Dr. Paul Brand of Vellore Christian Medical College. A grant of Rs. 25 lakhs (£187,500) is required for this purpose. For the purpose of the All-India effort to detect and treat 2 million cases of leprosy, each State Government will need a good leprosy organization. The finance of the Third Plan is visualized at Rs. 1,700 lakhs (£12,750,000).

20. DR. H. K. LALL gave a paper on the *Control of Leprosy*. He reviewed the history of leprosy control in the past 40 years and warned that future control will not be too easy in spite of the possession of the sulphones. These should be used in mass treatment campaigns, with intensive surveys to detect early cases, and with education and propaganda not getting ahead of treatment. In propaganda we would be wrong to say leprosy is not at all infectious but try to keep away from extremes and on the right lines as the truth is revealed. Nor should we denounce segregation, as it has some value, notably the idea of night segregation. It is very important to have the right type of personnel, both medical and auxiliary. For the time being it is best to have a separate leprosy cadre.

21. SHRI M. B. DIWAN also gave a paper on the *Control of Leprosy*. He said that India can control leprosy in a reasonable period provided that we adopt a sane, practical, and scientific attitude towards the problem and obtain personnel who are devoted, intelligent, and properly trained. Also the programme should be carried out on a broad front without a break, with open mind to

adopt all possible improvements, and with periodic assessments of progress. The sulphone treatment has great advantages, but it is neither specific nor bacteriocidal, and it can fail so that relapses occur and it is still not certain that it is of value for prophylaxis. Control by treatment alone, with isolation abandoned, is an attitude not scientific. However inconvenient or expensive, we cannot dispense with isolation. In a sympathetic prepared atmosphere voluntary isolation is quite practicable. There is still ample scope for the creation of new leprosy institutions with their special contributions, and the leprosy control scheme should use all good measures. More emphasis on educative programmes is much needed. Even among medical men and the educated classes prejudice against leprosy exists, and it should be broken down. Non-medical auxiliaries do most of the work in the present control schemes, and their selection and training needs to be improved. Voluntary associations should be welcomed to join in the leprosy campaign.

22. MR. W. BAILEY gave a paper on *A Work of Reconstruction.* He defined rehabilitation and to the medical, social, and economic aspects he added the spiritual, for our ministry is to the whole man. So far there is a gulf between occupational and rehabilitation therapy, and these two should be brought together. There are four main groups of ex-patients, those who are incapable of work, those who can be taught to work in spite of their deformities, those who need training for a new job, and those who need help in finding a suitable job. He calculates that there may be about half a million leprosy ex-patients in India who cannot do economic work; some 855,000 capable of open competitive work, and some 165,000 capable of doing profitable sheltered jobs. Rehabilitation should begin to be thought of and planned right from the beginning of the patient's treatment, and the aim should be a co-operative effort between surgeon, social worker, business and industry. The leprosy patient should never need to become a beggar. He can become a useful citizen again.

23. DR. I. SANTRA gave a paper on *Social Aspects Including Rehabilitation.* He said that social service should be based on religion, and the impulse to leprosy work in India came from religious people and was approved by a saint (Mahatma Gandhi). In India there are at least 1,500,000 leprosy cases, out of which 300,000 may be infectious, and many are blind or deformed. The people should be educated to recognise the disease and to know about its curability and degree of infectivity. Cured cases must be received back into the community and we have to prepare both the patient and the community for that. Children of infective patients should be separated and given proper training to fit them for their own life. The provision of better food for the masses is very important. In India there is a greater incidence of leprosy where the food level is low.

Rehabilitation should be a part of the work of every leprosy scheme.

24. DR. S. D. GOKHALE dealt with *Social Aspects of Institutional Treatment*. There is need of careful study of the family structure and social relationship among the leprosy patients. Many of them beg, not perhaps of their own choice, but because they have no home and no other means of subsistence. It is mostly disfigurement which drives a leprosy case out of the community. For those with major disfigurement the social worker has a heavy job, for they need shelter, occupation, and good food. A leprosy beggar however may not want to be rehabilitated, and this problem needs special attention, which the author thought calls for special institutions, in which they can be handled with sympathy and understanding, and psychiatric therapy will be called for, as well as good counsel. There should be careful selection of vocations and jobs. The children of leprosy patients should be cared for, those infected as well as those free of the disease.

25. SHRI H. SHAMRAU gave a paper on *Leprosy Control*. In leprosy surveys it is best to start with treatment and propaganda and then deepen and widen the survey work. There should be an All-India Leprosy Board at Delhi with branches in each State. Each leprosy scheme centre should have a medical officer, pharmacist, laboratory technician, and 8 to 10 paramedical workers, social workers, peons, sweepers, and a van driver, and 2 clerks for the office. Each centre needs a well-equipped mobile medical van, bicycles, and staff quarters. The centre should be placed in or near the district headquarters. Many treatment centres should be opened to which no patient should be made to walk more than 3 miles. Domiciliary treatment should be used as necessary, and the work of the auxiliary staff should be supervised by the medical officer. Advice on segregation and prevention should be given, and education of the public. Work by the patients should be encouraged and guided and rehabilitation schemes set going.

26. DR. M. MASIH gave a paper on *An Effective Approach to the Leprosy Problem*. The old dread of leprosy is yielding to advancing knowledge of its mild infectivity and curability, and it could easily be treated in general hospitals and dispensaries. It might be possible to attach special wards to these, but doctors should be adequately trained in all medical schools. Local bodies should take an interest in the leprosy campaign and share in it, and more emphasis should be laid on rehabilitation. More centres are needed for this, whether in older leprosy homes or specially established.

27. SHRI T. N. JAGADISAN spoke on *The Principles and Practice of Rehabilitation in Leprosy*. He said there is a great rise in the interest in this, and gave a list of the existing literature, and described the many institutions in India which are now actively engaged in rehabilitation work. He warned against accepting agriculture in

every case as the ideal work for the leprosy patient: in many cases it is too heavy or too traumatic. Rehabilitation should be suited to every patient, and physiotherapy, surgical corrections, psychotherapy, social integration, public propaganda and persuasion, and preventive medicine and individual care enter into the whole task. It is a huge task but we should not despair, but learn from the domestic mouse "which bites away a huge bulk bit by bit".

28. DR. P. SEN read a paper on *Social Factors Demand Adequate Attention*. Since May 1958, he had studied the social aspects of leprosy to provide a basis for a mass educational programme for Savda, East Khandesh. He soon found there was need for training in social aspects to be given to the field workers and medical officers of the national leprosy control programme. These social factors hinder prevention and treatment and even influence the causation of leprosy. The environmental social factors which influence causation are poverty, poor housing, starvation, squalor, ignorance of the rules of health, and community prejudices. Even emotional disturbances may react adversely on leprosy. The fear and hostility and apathy of the other members of society also react adversely. As for the victim of leprosy, he is denied the means of livelihood, denied family and social life, even denied hospital facilities for the treatment of other diseases. He is often denied facilities for rehabilitation when the disease is arrested. Even the law is against him, for by the Hindu Marriage Act of 1955 leprosy of 3 years' duration is a cause for divorce.

Patients naturally react to all this by being reluctant to accept the diagnosis of the disease, by concealment of the disease, by depression and drift towards suicide, by loss of mental and moral fibre, by irregularity in taking treatment, by forced reliance on begging or private charity. These things tend to make the disease worse and delay cure.

The patient's family also suffers, especially from loss of the wage-earner's income, and from the discrimination against the children in education and marriage.

All these things come back on society in economic and social loss, and the ravages of the social stigma are as much as the disease itself. As much study and effort to counteract these social factors will be needed as studies in therapy and surgical correction of the disease.

29. MISS T. SURTY gave a paper on *Education*. She gave an account of organised educational work in leprosy carried out in Greater Bombay. The plan of work includes posters for hospitals, clinics, bus stands, schools and colleges, railway stations, dispensaries, and exhibitions. Written material for publication comprised material for newspapers and magazines, medical journals, and goodwill advertisements. Folders, leaflets, and booklets were prepared for patients and relatives, schools and colleges, and

exhibitions. Lectures, seminars, and talks were arranged for doctors and students and welfare and other organisations. Films are made for schools and colleges, cinemas, mills and factories, and for showing in endemic areas. Radio talks are obtained, and models, charts, and posters made for stalls in exhibitions. Three types of film documentaries are aimed at; (*a*) for students, a film showing a variety of early lesions and precautionary measures; (*b*) for cinemas, a film with a story with a human appeal, without depicting the advanced type of leprosy; (*c*) for the masses in endemic urban areas, a film showing early lesions leading to advanced stages, and the results of treatment, and precautionary measures. It is difficult to get the full cooperation of the press, as editors are more interested in the spectacular than the educational. One should not overlook the aesthetic appeal of attractive colours in posters and leaflets.

30. DRS. P. SEN and I. O. DESHMUKH gave a paper on *An Epidemiological Survey of Social Behaviour Towards Leprosy*. From almost all centres in the national leprosy campaign comes the report that a large number of patients do not attend well for taking the sulphone therapy, and remain indifferent to treatment. Hence the Hind Kusht Nivaran Sangh undertook an investigation at Savda through a special medical social scientist, Dr. P. Sen. He prepared 2 questionnaires, one for the patients and one for the general population, and it was found that most of the patients and the public were totally ignorant of the elementary scientific concepts of leprosy, that they have an elaborate set of ideas and beliefs about leprosy inherited from the past which are utterly useless in active control of leprosy, that there is excessive ostracism in social behaviour towards leprosy patients. In the beginning of the work at Savda the subsidiary clinics of the Centre had to be carried on at the roadsides or in the fields as village leaders would not permit them near human habitations. People in general and the village leaders and social workers avoided any contact with the workers of the Centre for fear of having to assist in case detection. People got annoyed if the workers visited their homes even on a courtesy call, lest their neighbours suspect they had anyone suffering from leprosy. The attitude of the medical practitioners in the area was not helpful. Since the social study was begun, there has been much improvement in the general atmosphere, with much cooperation, and the clinics have been rescued from the roadside and fields and brought in to dispensaries and offices. It shows how essential are publicity and health education.

B. *The Kondhwa Leprosarium, Poona District Leprosy Committee*

This leprosy hospital was founded in 1910 and handed over by the Government of Bombay to the Poona Leprosy Committee in 1956. Under the care of the President, Dr. N. J. Bandorawala, and the Vice-President, Maj. Gen. B. Basu, and a very keen medical staff

it has made very notable progress, not only in buildings, industries, and general administration, but has taken a leading part in the wave of advanced plastic and reconstructive surgery which happily is spreading over India and in which India leads the leprosy world. Dr. Paul Brand of Vellore and Sir Harold Gillies of London might be described as the inspirers and guides and their able pupils have voluntarily worked at Kondhwa with highly satisfying results. These were Dr. N. H. Antia, Dr. P. K. Bharucha, Col. B. B. Choksi, Dr. G. N. Khatri. The Editor in December 1959 had the privilege of a visit to Kondhwa and attests the amazing lift in morale there as the result of the work of these surgeons. Kondhwa could easily become a training centre for plastic and reconstructive surgery. There is a resident physiotherapist, Mr. W. Jennings. On the medical side there is also an equally high standard, under Dr. B. B. Gokhale and Dr. S. V. Marathe. There are many honorary workers as well as the permanent staff. Medical research could also develop profitably in Kondhwa. There are about 300 inpatients. The total budget is around £7,500.

The dynamic happy state of the work at Kondhwa was a revelation to the visitor. It seems it is due to; (*a*) the wisdom of Government in handing over the work to a civic committee led by Dr. Bandorawala and Maj. Gen. Basu, every member of which committee is enlightened about leprosy and experienced in some section of community service; (*b*) the introduction of physiotherapy, plastic, and reconstructive surgery which revealed to the patient that surgical relief would be added to medical relief, and that the patient was an individual whom his fellow-citizens thought worth the rehabilitation; (*c*) the extraordinary outpouring of voluntary service by the citizens and by the specialist physicians and surgeons.

Correction

The postal address of the East African Leprosy Research Centre was given incorrectly on p. 68 of the "Leprosy Review", January, 1960. It should be P.O. Box 1044, Busia, Uganda.

Attempts to Obtain Mitsuda Reactions in the Skin of Leprosy Patients, using Fresh Suspensions of Nodules Produced in Black Mice by Inoculations of *M. leprae:* Greatly Increased Virulence of *M. leprae* by Passage through Black Mice

(with an Addendum on work using Boiled Inoculum)

H. C. de SOUZA-ARAUJO, M.D., Dr.P.H.
Professor of Leprology, Medical School,
University of Rio de Janeiro

FUMIO HAYASHI[1] continued the work of KENSUKE MITSUDA on skin tests with human lepromin in leprosy patients, and reported in 1933 that the reactions produced by boiled and unboiled lepromins, which he called vaccines, showed no difference. In a great number of leprosy patients I used living or dead suspensions of bacilli from human and rat lepromas, and confirmed the finding of HAYASHI.

This year I succeeded in obtaining the transmission of infection by *M. leprae* to black mice of American race, and produced subcutaneous nodules with lepromatous structure, or abscessed lesions. Such nodules I triturated and diluted in saline, and used the unboiled suspension as the antigen for skin tests, similarly to my previous use of boiled and unboiled suspensions of murine and human lepromas, and cultures of *M. tuberculosis.*

In the present experiment I used 7 volunteers, of whom 3 were lepromatous cases and 4 neural. On 1st September 1959 I inoculated each patient with 0.15 to 0.2 ml. intradermally of the said suspension, the site being the antero-lateral aspect of the left thigh. The patients were followed up over 70 days, biopsies were taken of their lesions on one or two occasions for study of bacteriology and histology, and the bacteria were also studied in the skin sera and nasal mucosa for comparison.

Material and Methods and Case Notes

One out of 8 black mice inoculated 3 July 1959 with suspension of human leproma (derived from Edgard, case 7) and showing a large subcutaneous inguinal nodule, was killed on 26th August at 53rd day after inoculation. The saline dilution of the triturated nodule was examined microscopically and kept for the inoculations and for electron micrographs. The inoculations were carried out as for the lepromin reaction.

Case 1. L.C. white male, aet. 70 years, leprosy patient since 1938, his disease having completed the "parabolic curve" of Muir, from A_1 to B_3 and A_2 within 40 years. He is now a "burnt-out" case, with bilateral high steppage gait (Scheube sign) and claw hands. There were innumerable bacilli and globi in smears from both sides of his nasal septum. This was on 29th August 1959, after he had taken Promin intravenously for 2 years without any improvement in his neural symptoms. On 1st September 1959 he was inoculated with 0.15 ml. of the inoculum from the black mice. On 5th September he had fever, and pain in the site, and an erythema 15 × 15 cm. in size. On 9th September the erythema reduced and nodulation began to form in its centre. On 24th September a biopsy of the lesion was taken at the third week. On 4th October four smears were taken

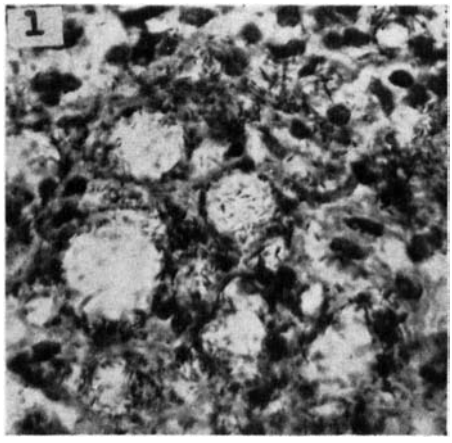


FIG. 1

Photomicrograph of a section of the leproma of Edgard B. used to infect the black mice on 3rd July, 1959. Stained by Z.N. 700 x.

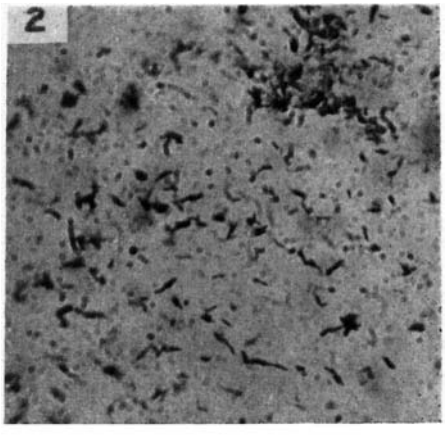


FIG. 2

Photomicrograph of the smear of the suspension of the nodule of the black mouse killed on 26th August and used as inoculum for the skin tests. Suspension unboiled. Stained by Z.N. 700 x.

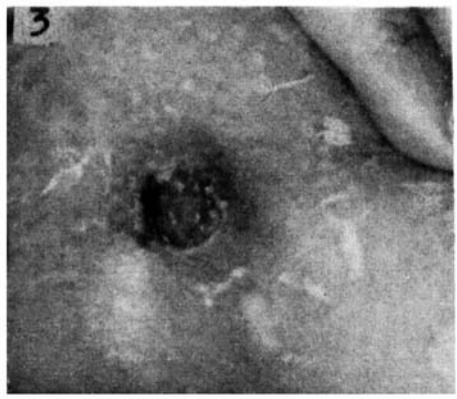


FIG. 3
Photograph of the lesion of patient 2 *after* 66 *days incubation: crater of* 1.5 × 1.5 *cm. upon an infiltration of* 3 × 4 *cm.*

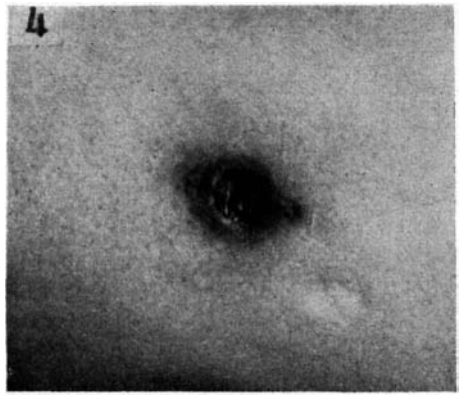


FIG. 4
Photograph of the lesion of patient 5 *after* 66 *days incubation: deep crater of* 2 × 1 *cm. upon an infiltration of* 4 × 4 *cm.*

from the lesion and from the nasal mucosa. On 17th October there was a small scar with a crust on a nodule 1 × 1 cm. On 24th October the nodule was small in size, at the 54th day after inoculation. On 5th November the lesion had subsided, On 14th November the nodule was 1 × 2 cm., but no exacerbation of symptoms. and a smear was taken of the nasal mucosa.

Case 2. A.B.A., a white female, aet. 45 years, leprosy patient, L_1 type, since 1953, when she had a few nodules on her legs and positive nasal mucosa. After a long period of standard treatment the skin lesions (lepromas and macules) disappeared and nerve signs started in both hands and feet. In 1950 she was N_2 and began with Promin treatment, but there was no improvement in the nerve signs. On 30th April 1957 she presented double claw hand, perforating plantar ulcers on both feet, and there were a few bacilli in the nasal mucosa. On 1st September 1959 she was inoculated with 0.15 ml. of the suspension derived from the black mice. On 3rd September she had fever, pain in the site, and erythema of 5 × 5 cm. locally. On 8th September nodulation in the site began. On 10th and 15th September the erythema was less and the nodule 1 × 1 cm. On 17th September there was infiltration of 3 × 3 cm. On 24th September a biopsy was taken of the lesion at the third week, and smears. On 10th October smears of the lesion were positive. On 24th October at the 54th day after inoculation the lesion was crateriform and bled easily. On 29th October the crater was 1.5 × 1.5 cm. in size, and smears were taken. On 7th November the crater was still open, and was photographed. There was no exacerbation of skin symptoms and no lepra reaction at all.

Case 3. R.C.R., white male, aet. 35 years. In 1957 he was L_1-N_1 with lepromas on both elbows, erythematous spots on both legs, impairment of sensation in arms, hands, and feet. Smears from skin and nose were positive for bacilli. He showed good improvement after 90 intravenous injections of Promin. On 1st September he was injected with 0.10 ml. of black mouse inoculum. On 3rd September he had fever and showed 10 × 10 cm. local erythema. On 5th September the erythema was regressing and nodulation had begun. On 9th September there was a nodule of 0.5 × 0.5 cm. and this increased by 15th September. On 22nd September, 3 weeks after inoculation, biopsy and smears were taken. On 29th September a crater had formed. On 1st October 4 smears were taken of the lesion and the nasal mucosa. On 27th October at 57 days after inoculation, there was a large crater with 2 cm. of detached skin around it, and the patient complained of pain. On 29th October new smears were taken, at a time when the lesion was regressing slowly. There was no exacerbation of skin lesions and no lepra reaction.

Case 4. G.W., white male, aet. 34 years, weight 126 kg. His father is a case of L_2 leprosy, and his mother had early leprosy years ago. On 20th August 1959 he showed an erythematous infiltration on left frontal region, which was positive for bacilli, as also the nasal mucosa. He also had axillary and inguinal eczema marginatum. He was given Promin treatment, with a good response. On 1st September he was injected with 0.2 ml. of the black mouse inoculum. On 3rd September he had fever and pain, an erythema of 10 × 10 cm., and swelling of left inguinal lymph glands which impeded his walk. On 5th September there was less pain and the erythema had increased to 20 × 20 cm., without a nodule. On 10th September there was an infiltrated swelling turning to nodulation. On 15th to 22nd September there was a hard infiltration of 10 × 10 cm. On 24th September, the 54th day, the infiltration had disappeared leaving a small scar with a slight secretion in its centre. There was no exacerbation of skin symptoms nor lepra reaction. A biopsy was taken of the experimental lesion.

Case 5. M.R., a white female, aet. 66 years, who had leprosy for 30 years as L_3 case. She became clinically cured but relapsed and is intolerant to sulphone. Now she is L_2-N_2 with widespread large elevated spots and perforating plantar ulcers in both feet, and skin and nose bacterially positive. On 1st September she was injected with 0.2 ml. of the black mouse inoculum. On 5th September she had fever and local pain and showed 5 × 5 cm. of erythematous infiltration. On 19th September there was an abscessed lesion of 5 × 5 cm. on the thigh. On 22nd September the third-week biopsy was taken, also smears. On 29th September pus was collected for bacteriology. On 6th October four smears were taken. On 17th October the lesion was better and the infiltration almost gone. On 3rd November smears were taken of skin and nasal mucosa. On 7th November, at the 67th day, the lesion was photographed. The ulceration was 2 × 2 cm. She complained of pains and the skin lesions were exacerbated.

Case 6. N.A., a female mulatto, aet. 34 years, L_3 case for 9 years. On 1st September she was injected with 0.2 ml. of the black mouse inoculum. On 13th October she complained of fever and had increased general pains for the last 2 weeks, with exacerbation of skin lesions. As she suffers constantly from lepra reaction it is difficult to accept that the situation is due to the inoculum. Biopsy was taken. Smears of biopsy at the margin of the lesion were strongly positive for acid-fast bacilli which is not important because she is a case of diffuse leprosy. On 14th November a 2 × 2 cm. black scar remained in the lesion. The scar was opened with the galvanic needle and compressed to obtain secretion for culture and bacilloscopy.

Case 7. Edgard B., white male, aet. 37 years, who in 12 years had taken about 15 litres of sulphones, mostly intravenous Promin. After a period of good improvement, for 2 years he has suffered periodic lepra reaction. Now he is a L_3-N_1 case, covered with plaques and large and small lepromas, and the nasal mucosa strongly positive for acid-fast bacilli and globi. About 6 months ago he started on 6 to 8 tablets of Ciba 1906, without change in the positivity of the nasal mucosa but with considerable change in the morphology of *M. leprae* from the skin. On 1st September he was injected with 0.2 ml. of the black mouse inoculum (the black mouse was infected on 3rd July 1959 with the patient's own leproma suspension). On 10th September there was nodulation of 2 × 2 cm. increasing to 3 × 3 cm. on 15th September. On 29th September in the 4th week after inoculation biopsy of the lesion was taken, and the secretion sown in culture media, and smears were taken. On 6th October the lesion was much better, with a crater of 1 × 1 cm. Four smears were taken. On 5th November the crater was reduced in size; smears were taken of the secretion of the lesion and nasal mucosa. On 7th November new biopsies were taken, and skin emulsion and nasal mucosal secretion inoculated in 15 black mice. Though this patient was an L_3 case he had stronger general and skin reactions with the inoculations.

Bacilloscopy

Smears taken from the lesion at 3 weeks were surprisingly poor in acid-fast bacilli, and mostly showed free nodules. The nasal mucosa was positive in only 2 out of 7 patients. The scars, or eliminating foci, were poor in purulent secretion and in phagocytised elements.

Histopathology

Biopsies of the lesions were made from all 7 patients, 4 being in the 3rd week after inoculation, 1 in the 4th, 1 in the 6th, and 1 in the 8th. The reports of Prof. C. B. MAGARINES TORRES (Chief of the Div. of Anatomopathology of the Oswaldo Cruz Institute). Reports Nos. 21,616 to 21,621 say "Moderate and discontinued infiltration by large mononuclear cells and lymphocytes around the superficial plexus of the subpapillary layer, and absence in all 6 specimens of nodules with tuberculoid structure". The material from one case (No. 6) was unsuitable for histological examination.

Comments

The dose of the inoculum was about 0.2 ml., which is the dose needed to infect mice of 20 g. weight. This dose was given to patients of an average weight of 60 kg. and it could be 3,000 times greater. The mice support 0.2 ml. of fresh emulsion of human leproma without ulceration of the skin (except in passage). The leprosy patients, whether their disease was active or quiescent, suffered a heavy local reaction, with crater formation, lasting for more than

2 months, and the final state is as yet unknown. Two hypotheses are under consideration, one of the great increase of virulence of *M. leprae* cultivated in the bodies of these murines, and the other of the hypersensitivity of the leprosy subjects. It is not easy to obtain volunteers for such experiments, but I shall try to repeat the test with boiled inoculum.

Conclusions

1. My impression is that *M. leprae* multiplied exuberantly in the black mice, increasing greatly in virulence, and this should be tested.

2. The living inoculum used caused strong local reaction in all 7 patients, which reaction differed clinically and histopathologically from that of the Mitsuda skin test.

3. These experiments should be repeated with boiled identical inoculum to allow of a definite conclusion.

4. The inoculated patients, save one, did not show the classical lepra reaction, but they will be observed further.

5. The lesions obtained in these 7 patients were comparable with those obtained with living cultures of acid-fast bacilli isolated from leprosy patients.

Addendum on later work with boiled inoculum

Following up the 3rd conclusion above, I prepared *boiled antigen* from a skin lesion of another black mouse of the same batch, and gave a dose of 0.2 ml. by intradermal injection in 11 adult persons, being 10 leprosy patients and 1 contact, with the following results:—

Case 1. L.C., male aet. 70 years (the same as No. 1 of the previous experiment). On 24th December he was inoculated in both thighs. On 26th December there was an early reaction and on 31st December regression. After 2nd and 3rd weeks both sides reactive and positive for bacilli.

Case 2. A.B.C., female aet. 46 years (the same as No. 2 of the previous experiment). On 3rd December she was inoculated with 0.15 ml. below the previous crater, which was still open. There was a strong reaction. By 14th January the crater reduced to 2 sq. cm. The lesion was positive for bacilli and the nasal mucosa negative.

Case 3. E.B., male aet. 37 years (the same as No. 7 of the previous experiment). On 5th December he was inoculated in his left thigh, 15 cm. above the previous lesion, which was still open, excreting abacillary pus. On 7th December at 48 hours there was a strong reaction, with erythema and infiltration of 5 sq. cm. On 12th December the infiltration had reduced to 3 sq. cm. On 7th January in the 4th week infiltration had reduced to 2 sq. cm. On 12th January there was abscess formation and positive smears for bacilli, also in nasal mucosa, +. (In November 7 was ++.)

Case 4. A.S., male aet. 67 years. He was L_3, now with only residual dark spots. The nasal mucosa is negative. Long ago he had repeatedly negative Mitsuda Test. On 3rd December he was inoculated with 0.2 ml. in the left thigh. On 5th December at 48 hours he showed infiltration of 3 sq. cm. and it so continued during 3 weeks. There was no pain. On 7th January the nodule ulcerated spontaneously. The Mitsuda Test was strongly positive clinically.

Case 5. R.R.C., black male, aet. 47 years. Was L_3 for many years and is now N_3. On 7th December he was inoculated in his left forearm with 0.2 ml. On 9th December at 48 hours it was negative, and after 2nd week positive ++. After 3rd week +++. On 7th January the nodule ulcerated, smears positive +, and nasal mucosa negative.

Case 6. M.N.C., female aet. 25 years. She was L_3 case, now bacterially negative. On 5th December was inoculated with 0.15 ml. in left thigh. On 7th December at 48 hours there was an erythema upon a hard infiltration of 10 sq. cm. On 31st December there was a large nodule and incision and aspiration were carried out. Bacilloscopy ++. On 7th January there was a scar of 0.5 sq. cm. On 14th January there was slight ulceration of 0.5 sq. cm.

Case 7. J.A., female of 45 years. L_1-N_1 case. The previous Mitsuda Test was slight +. On 3rd December she was inoculated in the left thigh with 0.2 ml. On 5th December at 48 hours was negative. After the 4th week there was erythema and infiltration. On 5th January the nodule opened. Bacilloscopy ++. On 12th January there was suppuration. On 14th January appearance of a good positive Mitsuda.

Case 8. E.R., white female of 65 years. L_2 case. On 7th December was inoculated with 0.2 ml. in left thigh. After 1 week there was erythema of 3 sq. cm. On 29th December erythema was reduced. On 5th January the infiltration was reduced. On 12th January no nodule formed.

Case 9. H.L., white male, 58 years. L_3 case. On 11th November 1959 the Mitsuda test was negative (Prof. H. Portugal). On 3rd December he was inoculated with 0.2 ml. in each thigh. On 5th December at 48 hours, negative and remained so up to 14th January.

Case 10. A.G., white female, L_2 case 2 years ago, since 1 year becoming a neural case with great enlargement of the left cubital nerve and neuralgia in the right foot. Bacilloscopy of the cubital nerve ++. Nasal mucosa + on both sides. On 24th December she was inoculated with 0.2 ml. in her left thigh. On 26th December at 48 hours, negative, and up to 14th January negative.

Case 11. H.G., white male of 35 years, husband of above case No. 10. On 24th December was inoculated with 0.2 ml. in left thigh. On 26th December at 48 hours, doubtful positive. On 14th January, +. After 3 weeks became Mitsuda -positive.

Comments

Five out of 10 leprosy cases, N_2 and N_3 type, gave a positive + test. Two L cases in frank regression gave one +, suspicious. Three L_2 and L_3 cases gave completely negative test and 1 adult contact of active leprosy gave mild positive + test.

Conclusion

The boiled leprotic antigen derived from the black mouse gave results not different from the classical Mitsuda Test. The patients will be observed further for some time in order to allow of definite assessment.

References

1. FUMIO HAYASHI, "Mitsuda's Skin Reaction in Leprosy", *Internat. J. Lep.*, **1**, 1, 1933, pp. 33-38.

STUDIES IN PLANTAR ULCER IN LEPROSY

V. The Complications of Plantar Ulcer

E. W. PRICE, F.R.C.S.E.
formerly Orthopaedic Surgeon, Leprosy Service, Eastern Nigeria

The complications of plantar ulcer in leprosy are important not only because they often lead to failure of treatment, but also because they may cause permanent damage to the foot. The neuropathic (Charcot) joint is also included in this study because it occurs frequently in feet with plantar ulceration.

The dominant features of complicated ulcer are infection and oedema. The infection may involve not only bone and joint, but also venous and lymphatic channels. Chronic oedema accompanies infection, but it may exist apart from infection as in the oedema of disuse or of derangement of the autonomic system.

It is important to recognise the persistence of oedema, because the condition retards the normal healing processes and can of itself lead to chronic fibrosis of the subcutaneous tissues.

The common complications of plantar ulcer are now described.

Subcutaneous Plantar Infection

The lesion which precedes frank ulceration of the sole is sterile until the skin is broken. When infection occurs—as a result of a crack in the dermis, or frank ulceration—subcutaneous banal infection is inevitable, and resembles the common infections of the palm of the hand. The recognition of infection without ulceration is important in case it is confused with the early sterile stage of the deep plantar necrosis which precedes ulceration in a neuropathic foot. Failure to distinguish the two lesions can lead to incision of a "necrosis blister" in mistake for a pocket of pus, an error which can initiate a train of events ending in bone and joint infection. (Fig. 3.)

In both lesions, there is a localised swelling which is tender to pressure and, as in the case illustrated, there may be superficial cracking of the skin suggestive of a portal of bacterial entry.

Deep necrosis, however, is preceded by several days—or nights—of continuous burning pain and heals rapidly with simple rest and elevation of the part. Deep infection is more painful and throbbing than burning; increased local warmth may be detected, and it does not respond to simple rest and elevation without antibiotic therapy. If in doubt, it is wise to rest the foot in an elevated position and use antibiotics. A swelling that persists painfully for 48 hours without improvement is then probably purulent, but it is still better to aspirate for diagnosis than to make a mistaken incision. The aspirated fluid is sterile from a necrosis blister and will show bacteria and leucocytes in cases of infection.

Bone and Joint Infection

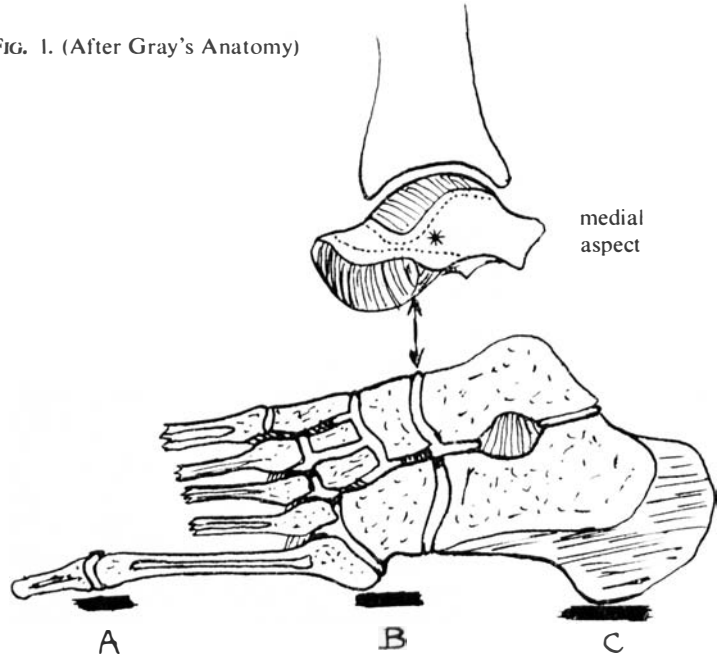
This is the tragedy of plantar ulceration. Once established it may remain incurable long after the leprosy is arrested; every effort should be made to avoid it, or recognize and treat it at the earliest possible moment. Symptoms are often masked by the associated anesthesia and it is wiser to rely on regular foot inspection for diagnosis, than on the patient coming of his own accord to seek treatment.

In the anesthetic foot, the extent of the infection is commonly more widespread than appears clinically and the futility of local metatarsal excision is often confirmed by radiology—which demonstrates wider spread of infection than is suspected at operation.

The site of the initial necrotic lesions before infection occurs is shown in Fig. 1. This lies under a metatarsal head in the forefoot (or under the head of the proximal phalanx of the big toe); mid-laterally, it lies under the tuberosity of the fifth metatarsal; and at the heel, under the lateral tuberosity of the calcaneum. The two latter bony points present prominently in the sole when there is weakness of the evertors of the foot.

The risks of pyogenic infection are seen from the diagram:

FIG. 1. (After Gray's Anatomy)



Oblique section of foot to show relation of joint spaces to sites of plantar ulceration
A, B and C represent the common sites of necrosis blister. If ulceration occurs, the underlying bone and joint are exposed to the danger of infection.

The ankle-joint is presented in mirror-image to show how closely the synovial membrane of ankle and talo-navicular joints approach on the medial aspect of the neck of the talus. Only "thin and indefinite capsular fibres" separate the joints (Frazer).

The mid-lateral lesion (B) is seen to be the most dangerous to the foot.

The forefoot ulcer: (A)

This exposes the metatarso-phalangeal joint and adjacent bones. Spread to adjacent joints is not an early event, but osteomyelitis readily spreads up the metatarsal and may lead to pathological fracture or involvement of the tarso-metatarsal joints.

The mid-lateral ulcer: (B)

This is the most dangerous of the lesions. It is a risk to both the cubo-metatarsal and the cubo-calcaneal joints. Spread from the cubo-metatarsal readily involves all the tarso-metatarsal joints except the first; then by continuity, the complex surfaces between the navicular and cuneiform bones. There is often disorganisation of the midfoot.

Cubo-calcaneal infection continues across the foot and invades the talo-navicular and anterior talo-calcaneal joints.

This exposes the ankle-joint to danger because of the surprising anatomical fact that the ankle-joint is separated from the base of a mid-lateral plantar ulcer by tissues which barely exceed 5 mm. in total thickness. Frazer (1946) points out that the synovial membranes of ankle and talo-navicular joints are separated on the medial side of the neck of the talus "only by thin and indefinite capsular fibres".

Clinically, there is often non-infective effusion into the ankle-joint due to the irritation of adjacent sepsis; the swollen ankle then raises the possibility of a neuropathic joint unless its nature is appreciated.

The Heel Ulcer: (C)

This involves the calcaneum only, until the later stages of infection; but it is important because the associated decalcification weakens the attachment of the long plantar ligament. Widespread involvement of the calcaneum is inevitably followed by collapse of the arches of the foot.

This disaster is represented clinically by an irregular pad of plantar tissues representing the sole of the foot, and by a new series of bony prominences in the sole over which pressure ulcers may develop. (Fig. 4.)

In collapse of the *lateral longitudinal arch*, these bony knuckles lie on a line passing across the foot from the tuberosity at the base of the 5th metatarsal towards the medial tuberosity of the calcaneum (Fig. 2). If this line is divided into three equal parts, the bony prominences are:

1. The tuberosity of the cuboid.
2. The anterior tubercle, or keel, of the calcaneum.

The resulting plantar ulcers (Fig. 5a) may join to form a linear ulcer passing medially from front to back across the posterior half of the sole (Fig. 5b).

Collapse of the *medial longitudinal arch* indicates a grosser damage to the foot. The bony prominences that may present in the sole are (Fig. 4b):

1. The insertion of peroneus longus into the base of the first metatarsal.
2. The insertion of peroneus longus into the 1st cuneiform.
3. The tuberosity of the navicular.

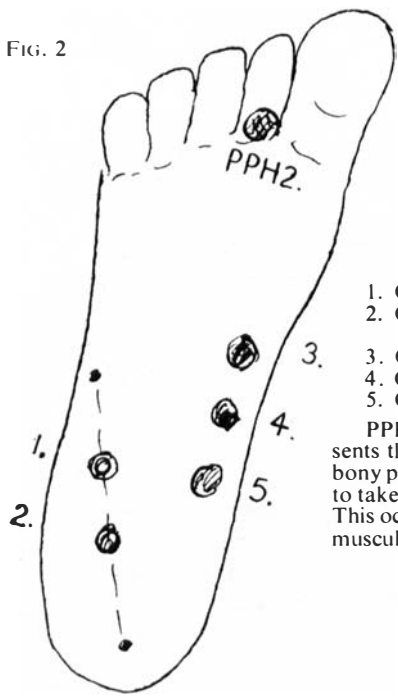
The clinical lesion is a series of ulcers, or a linear ulcer from the base of the 1st metatarsal to the medial aspect of the heel.

The final stage of tarsal disorganisation is represented by an indeterminate ulceration in the mid-sole (Fig. 5b left foot).

The additional plantar ulcers that may appear as a result of major damage to the bony architecture of the foot are represented in Fig. 2. Note that in extreme cases, there may be a pressure ulcer over the head of the proximal phalanx of the second toe.

Plantar Ulceration in Collapse of the Longitudinal Arches of the Foot
The diagram lists the sites of plantar ulceration which represent collapse of the longitudinal arches as follows:

FIG. 2



1. Overlying the tuberosity of the cuboid.
2. Overlying the anterior tubercle (keel) of the calcaneum.
3. Overlying the base of the 1st metatarsal.
4. Overlying the medial cuneiform.
5. Overlying the tuberosity of the navicular.

PPH2 (Proximal Phalangeal Head 2) represents the ulcer that sometimes occurs over this bony prominence when the second toe attempts to take over the walking function of the big toe. This occurs when there is failure of the intrinsic musculature of the big toe.

Phlebo-thrombosis and Chronic Lymphoedema

The patient with a chronically swollen lower leg is a frequent sight in leprosy settlements, and the infrequency with which this crippling complication is treated suggests that its nature is not always recognised. The lesions are disabling and permanent but can

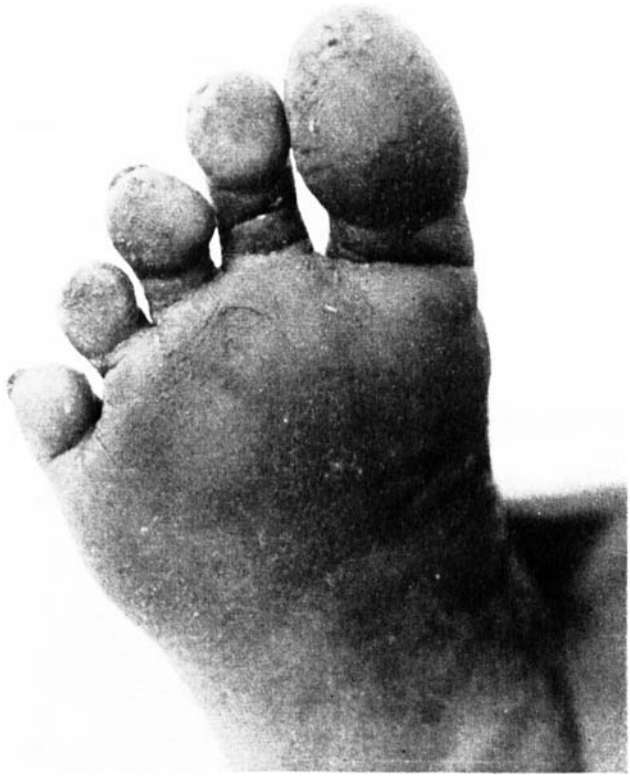


FIG. 3

Infection or Necrosis?

The swelling over the 4th metatarsal head may be an infection or a deep necrosis blister. If a blister, it will heal with simple rest and elevation. If infection, antibiotics and evacuation of pus are needed. The patient did not complain.

The lesion subsided with rest and elevation after four days, without an antibiotic. It is a necrosis blister. Ill-advised incision would have risked a chronic ulcer or subcutaneous banal infection.

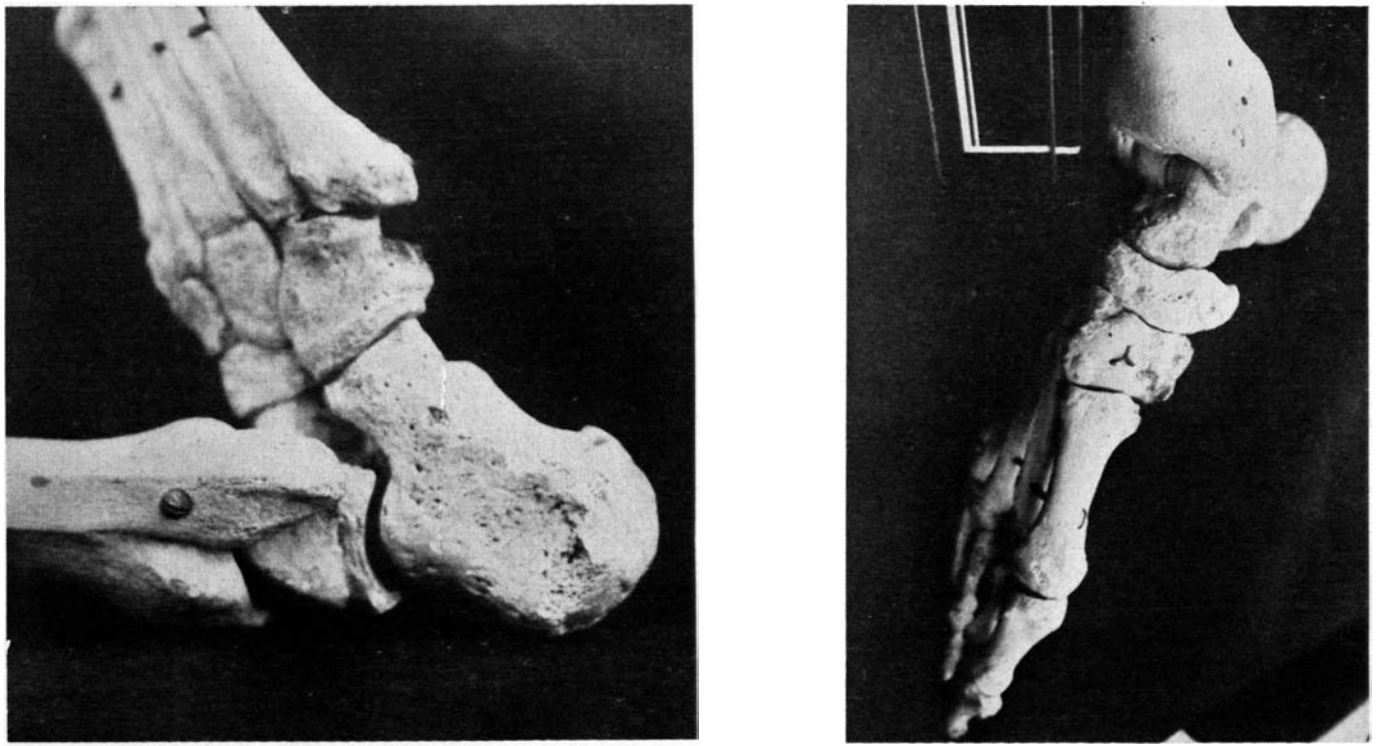


FIG. 4. *Collapse of the longitudinal arches*

(*a*) In collapse of the lateral arch the abnormally presenting bony points are the tuberosity of the cuboid, and the keel of the calcaneum (anterior tubercle). These lie in a line from the tuberosity on the base of the 5th metatarsal to the lateral tuberosity of the calcaneum.

(*b*) In collapse of the medial arch, the presenting bony prominences are the base of the 1st metatarsal, the tubercle on the medial cuneiform, and the tuberosity of the navicular.

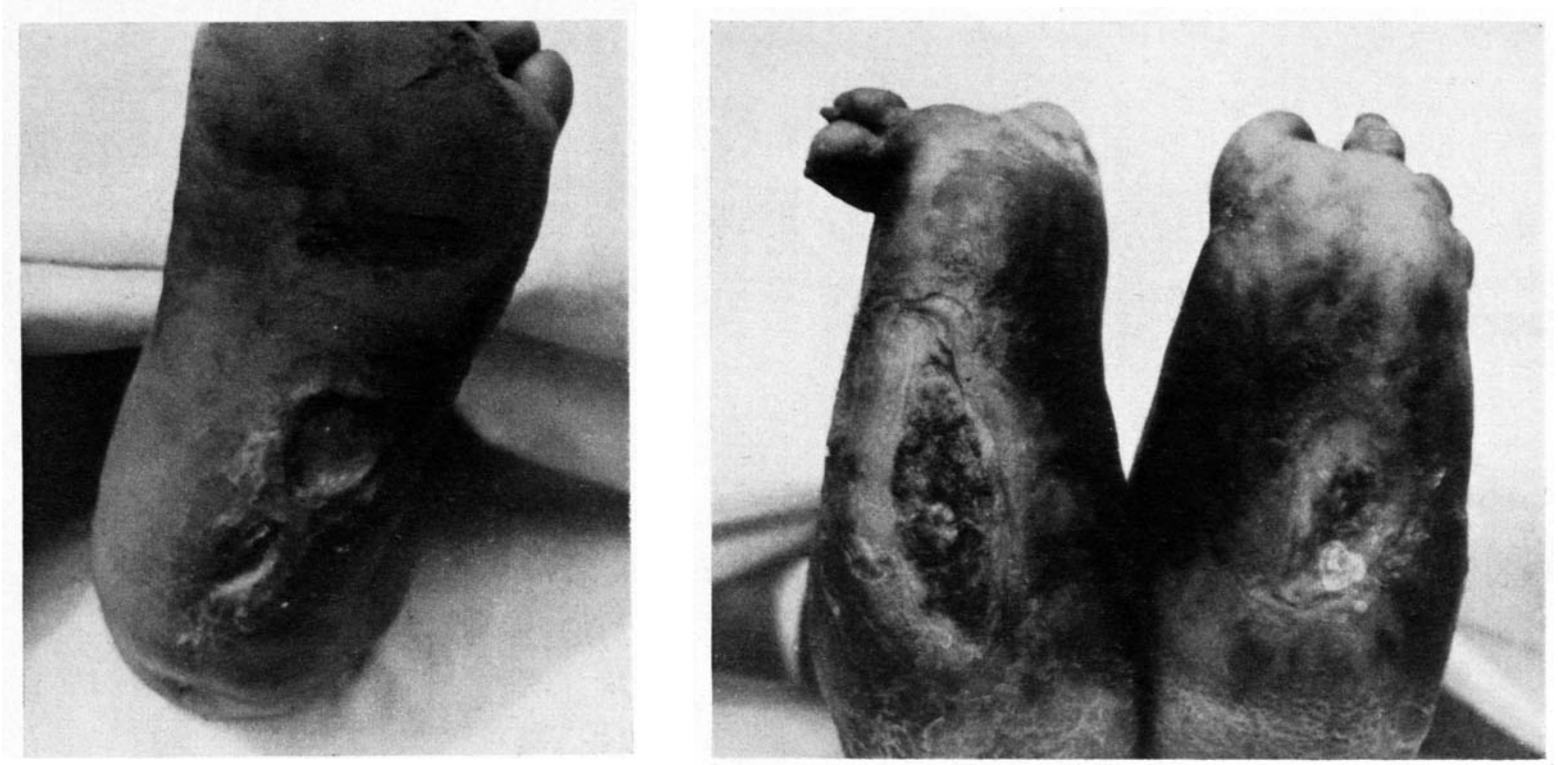
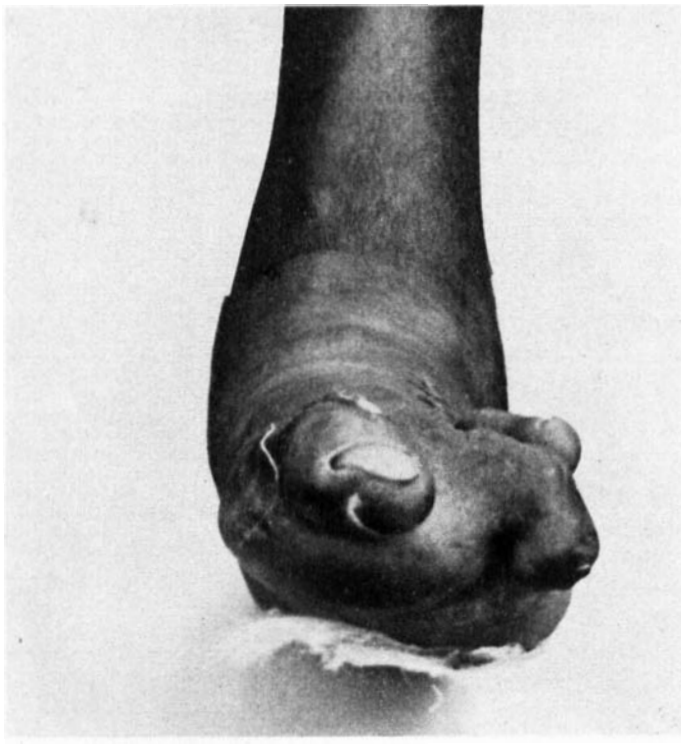


FIG. 5. *Ulceration from collapse of longitudinal arches*

5a. Collapse of the lateral arch results in ulcers along a line from the base of the 5th metatarsal to the lateral half of the heel. In this case, the calcaneum is partly destroyed and the ulcers overlie the tuberosity of the cuboid and the keel (anterior tubercle) of the calcaneum.

5b. Right foot: The individual ulcers of the previous illustration may fuse into a linear ulcer representing complete collapse of the lateral longitudinal arch. Left foot: When there is complete disorganisation of the foot, the plantar ulcer is an indefinite lesion over the presenting pad of tissues in the middle of the sole. (See left foot in 5a.)

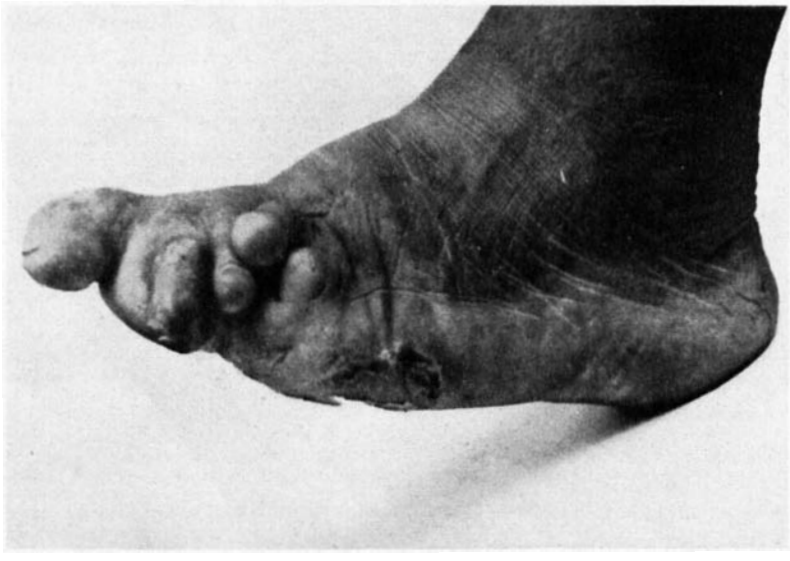


ANTERIOR

FIG. 6. *The disastrous results of metatarsectomy*

The gross deformity of the foot makes the fitting of footwear impossible without further operation; and it will be noted that the ulcer for which the operation was performed is still present. It is suggested that the operation be abandoned in the treatment of chronic plantar ulcer.

LATERAL



be avoided or treated, if the possibility of venous or lymphatic blockade is kept in mind.

The usual cause is neglected septic infection of the foot. Secondary phlebitis or lymphangitis occur, at first acutely or subacutely; but each recurring attack is less obvious clinically until the gross lesion of phlebo-thrombosis or chronic lymphoedema below the knee is established.

Phlebo-thrombosis of the foot and lower leg starts in the vicinity of the ulcer and spreads along the deep channels into the calf. The valves are incorporated in the clot, so that when the vein is recanalised (as is usual after a year or so), the venous channels lack valvular support. Chronic venous stasis ensues and the "post-phlebitic syndrome" is established (DeCamp et al. 1952). The acute attack of phlebitis may pass unnoticed, but usually there is pain and swelling of the calf and sole. There is fever. The oedema of the first attack may completely subside, but becomes more permanent with each fresh attack until it hardens into a firm non-pitting swelling of the lower leg.

The skin becomes ill-nourished and indurated, and may be eczematous. An indolent ulcer is not uncommon above the medial malleolus, and must not be mistaken for one which is leprotic in origin. The venous stasis of the sole hinders normal healing processes and predisposes to a subsequent inflammatory phlebitis. Infective emboli are very uncommon.

Chronic Lymphoedema, or chronic lymphatic blockade, is an entity distinct from phlebothrombosis and is much less common. During an acute attack, the oedema of the dorsum of the foot is associated with visible lines of tender lymphatic channels.

Repeated attacks produce an increasing induration of the skin and subcutaneous tissues, common to other forms of elephantiasis.

The venous circulation is unimpaired and the healing processes of the sole are relatively unaffected.

Both conditions have been observed during the course of chronic plantar ulceration in leprosy, and the importance of their early recognition and treatment is stressed in order to avoid the crippling effects of permanent lymphatic or venous damage.

The lesions occur in other diseases and are described more fully by Anning (1952), Monro (1952), Gibson et al. (1950), Cannon (1950), Watson (1953) and Ochsner et al. (1952).

Chronic Oedema of Disuse

The lower limb depends on activity, even more than the upper, to maintain lymphatic and venous circulation. A neuropathic foot often leads to an inactive shuffling gait and this is emphasised if there is plantar tenderness. It is possible that nervous involvement of the autonomic system is superadded.

The total effect is a tendency to oedema of the foot, and this may be limited to the sole in the early stage. The importance of the condition lies in the decreased resistance to infection and trauma that it encourages; and the care of the neuropathic foot must include the recognition and treatment of disuse oedema.

The lesion will be recognised during routine examination of the feet, but will be missed in the early stages unless the sole is palpated and pitting oedema sought. There are no other early signs, except for slight splaying of the toes. The leprosy worker will be aware that a similar condition is noted on the sole of both feet in cases of lepromatous leprosy, but the slight swelling of the sole and splaying of the toes is not accompanied by pitting oedema.

Recognition of the condition calls for the institution of treatment aimed at increasing the circulation and decreasing the debilitating effect of chronic oedema on the tissues of the sole.

The Neuropathic (Charcot) Joint

The neuropathic joint of leprosy resembles the lesion seen in diabetes rather than the classical "Charcot joint" of syphilis. In the absence of radiological facilities, its frequency is underestimated, but it should be suspected in every case of anaesthetic leprosy presenting unexplained painless or moderately tender swelling in the tarso-metatarsal region or at the ankle-joint. Walking is often unaffected.

Unrecognised and untreated, the condition develops slowly and progressively to disorganisation of the foot.

A neuropathic joint is often associated with plantar ulceration, as in diabetes (Martin 1952). In these cases, it may be difficult in an anaesthetic foot to determine whether a tarsal swelling is due to spreading infection or early neuropathy. At the ankle the difficulty may be to distinguish the lesion from irritation of the ankle-joint in septic mid-lateral ulceration.

In the neuropathic lesion, no signs of inflammation or joint-fluid are present. X-ray shows generalised decalcification and loss of joint-space with fragmentation of the adjacent bone.

New bone formation is minimal, in contrast to the similar lesions in syphilis. The metatarsal atrophies and may show spontaneous fracture. As in diabetes (Martin 1953), the lesion also occurs in the absence of sepsis or any vascular condition.

Those unfamiliar with the condition should consult papers describing the similar lesion in diabetes, Bolen (1956), Bailey et al. (1947), Jacobs (1958). There appears to be no literature concerning its occurrence in leprosy.

Metatarsectomy

It is not usual to describe surgical intervention as the complication of a lesion, but the occasion is taken to draw attention to the

undesirable effects that follow a high proportion of cases subjected to this operation.

In general, partial metatarsectomy is performed in an attempt to achieve healing of a chronic plantar ulcer. The observation of a number of cases that have undergone this treatment makes it doubtful if the mutilation is ever really justified.

The deformity caused (Fig. 6) is often severe and necessitates further surgical correction if footwear is to be fitted. The ulcer for which the operation is performed may not heal, or may recur (as the illustration shows). Not uncommonly, another plantar ulcer appears elsewhere on the foot after the intervention, and even if the ulcer remains healed, the mechanics of the foot are permanently disturbed.

The most convincing argument against metatarsectomy is the knowledge that healing of a chronic ulcer can be achieved by other non-traumatic methods. It is therefore suggested that control of the complications of plantar ulcer will be advanced by the suppression of what is largely a useless and crippling procedure.

Summary

1. The complications of plantar ulceration are described.

2. It is recalled that plantar ulceration is itself a complication of a previous pressure necrosis of the sole.

3. The serious outcome of several of the complications is described and the importance of early diagnosis and treatment is stressed.

4. Attention is drawn to those complications not commonly treated in leprosy settlements: phlebothrombosis, chronic lymphoedema, disuse oedema, and the neuropathic (Charcot) joint.

5. It is suggested that metatarsectomy be considered an avoidable complication of plantar ulceration.

References

ANNING, S. T. (1952) *Lancet*, **263,** 789.
BAILEY, C. C. and ROOT, H. F. (1947) *New Eng. J. Med.*, **236,** 397.
BOLEN, J. G. (1956) *Radiology*, **67,** 95.
CANNON, B. (1950) *Postgrad. Med.*, **8,** 317.
DECAMP, P. T. and OCHSNER, A. (1952) *Postgrad. Med. J.*, **28,** 517.
FRAZER, J. E., "Anatomy of Human Skeleton" 4th Ed. (Churchill) 1946.
JACOBS, J. E. (1958) *Journ. Bone & Jt. Surg.*, **40A,** 1043.
MARTIN, M. M. (1952) *Proc. Roy. Soc. Med.*, **45,** 503.
MARTIN, M. M. (1953) *Brain*, **76,** 594.
MONRO, A. K. (1952) *Postgrad. Med. J.*, **28,** 455.
OCHSNER, A., DECAMP, P. T., and LANDRY, R. M. (1952) *Journ. Bone & Jt. Surg.*, **34A,** 741.
WATSON, J. (1953) *Br. J. Surg.*, **41,** 31.

A REPORT ON THE USE OF CHLOROQUINE SULPHATE IN LEPRA REACTION

K. RAMANUJAM, M.B.B.S.
Medical Officer, Government Silver Jubilee Children's Clinic, Saidapet, Madras, India

Introduction

Chloroquine sulphate, the latest and widely used synthetic anti-malarial, had shown in recent years greater spheres of its usefulness in the treatment of amoebiasis, taeniasis, rheumatoid arthritis and lupus erythematosus. The possible therapeutic usefulness of this drug in lepra reaction was first reported from a hospital for tropical diseases in Paris, where a woman leprosy patient in the grip of lepra reaction was thought to be suffering from malaria, and treated with chloroquine. The presence of malarial infection was disproved, but it was observed that there was a rapid amelioration of the symptoms of reaction on chloroquine. This observation was followed up and reported on favourably by other workers. THANGARAJ[1] using Camaquin brand of amodiaquin hydrochloride orally in a group of 11 lepromatous cases compared the result with two other groups of patients, one group of 13 cases treated with intravenous injection of potassium antimony tartrate, and another group of 14 cases as controls. As a result of this investigation he came to the conclusion that "Camoquin is effective in the control of acute lepra reaction in lepromatous leprosy" and that "it achieves its effect in less time than potassium antimony tartrate".

Another interesting observation about the usefulness of chloroquine came from MERKLEN and RIOU[2] who had reported that with concurrent administration of chloroquine, the reaction could be controlled without interruption of sulphone therapy. They added that combination of chloroquine and DDS was beneficial in bringing up the dose of DDS and in two instances chloroquine could be substituted for d-cortisone. They recommend a dose of 600 mgm. initially and then a maintenance dose of 300–400 mgm.; they considered that doses less than 200 mgm. a day were ineffective.

RAMU[3] reported symptomatic relief in all the 8 cases of lepra reaction he treated with chloroquine diphosphate. His dosage regimen was one tablet (equal to 250 mgm. of the base) three times a day for one week and later one tablet twice a day for another 2 weeks. The time taken for relief to set in under this regimen varied from 4 days to 14 days. He came to the tentative conclusion that chloroquine is a useful drug in the treatment of lepra reaction.

Object of the Study

Barring the oral administration of corticosteroids, the only effective treatment of acute lepra reaction has been the parenteral

administration of antimony preparations. With the extension of mass anti-leprosy treatment in endemic areas, more cases of leprosy come under medical surveillance and more cases of lepra reaction are bound to be detected. The accepted line of treatment for lepra reaction, namely the parenteral administration of antimony, offers certain practical difficulties in rural areas. Therefore the favourable reports on the effectiveness of orally administered antimalarial drugs in the control of lepra reaction have prompted this investigation.

The object of the investigation is two-fold: (1) To find out how effectively and in what period of time chloroquine sulphate is able to control lepra reaction and, (2) how far this drug will be useful in controlling the reactions which occur very frequently in a small number of cases, and so render almost impossible the institution of adequate anti-leprosy treatment.

Material for Study

Between March and September 1959, 27 cases of lepromatous leprosy who reported with lepra reaction of varying grades of severity were accepted for the investigation. This group included 2 cases who were almost in a state of perpetual reaction, which made them incapable of taking the leprosy treatment.

The Method

The cases for investigation were entered on a proforma along with the details of the patient's condition—such as the drug he was on, whether it was the first reaction or one of several; and also the symptoms and signs such as fever, joint pain, nerve pain, bodily pain, presence of rose-spot nodules, subcutaneous nodules, exacerbation of existing lesions, onset of new lesions, turgescence of the nasal mucous membrane and the condition of the ocular elements. Details of treatment given and the progress of the case from time to time was recorded.

"Nivaquine" brand of chloroquine sulphate was administered orally in doses of 400 mgm. twice a day, equivalent to 300 mgm. of chloroquine base. This dose was maintained till the symptoms showed a tendency to abate, and then it was tailed off to 200 mgm. twice a day and later on to 200 mgm. a day. The drug was discontinued once the symptoms and signs of reaction completely disappeared. In some instances, where "experienced" patients asked for the potassium antimony tartrate injections, chloroquine was given orally along with intravenous injections of 2 ml. of pyrogen-free sterile distilled water. This clinic being only an outpatient department, no four-hourly temperature charts were maintained; the patients carried away two days' supply of the drug at a time and when they reported again, an examination as to the patients' condition was made and an enquiry was also made with regard to any untoward

symptoms. As far as possible no leading questions with regard to the toxic symptoms due to chloroquine were put to the patient, but in a few instances it was necessary, because some of the patients as a matter of course attributed any adverse symptoms to the chloroquine. In a few instances, the patients discontinued tablets after taking them for 2–4 days. However, when they turned up again, their condition was noted although the chloroquine tablets had been discontinued in the meantime.

Results

For purposes of analysis of the results, the group of 27 cases of lepra reaction have to be split into two sub-groups—one of the 25 cases who had pure and simple lepra reaction and a small group of 2 cases who were in a state of almost continuous lepra reaction. The results obtained in these cases have been graded into three categories—"Relieved", "Improved" and "Failed". By "Relieved" it is meant cases where there is total relief from symptoms and signs of reaction; in the "Improved" cases although there was considerable relief, some remnant of the reaction syndrome such as mild neuritis or arthritis still persisted.

1. *In Acute Lepra Reaction:* Out of the 25 cases treated with Nivaquine brand chloroquine sulphate, 4 cases discontinued treatment for no special reason. Out of the balance of 21 cases, nine showed complete relief, (42.86%) and twelve showed improvement (57.14%).

The duration of treatment varied from 2 to 14 days. In 3 instances the patients discontinued treatment after 2–4 days chloroquine sulphate therapy; but when they were seen again a week to 10 days after discontinuance, they showed considerable improvement. On enquiry the patients said that they did not ask for the tablets again because they had considerably improved. The average period taken for the control of reaction was 7 days.

2. *In Chronic Lepra Reaction:* Two cases of lepromatous leprosy who had been on oral DDS therapy for a considerable period with good results entered a state of frequent lepra reaction—a relentless recurrence of the reaction, whether any specific anti-leprosy treatment was employed or not. In one case (case No. 3) the reaction used to be quite severe and in the other case (case No. 14), apart from slight exacerbation of lesions and E.N.L. phenomenon, nerve pain was quite agonising. Both these cases were given chloroquine sulphate, beginning with 400 mgm. twice a day and then tailing off to 200 mgm. a day. In the first case where the chloroquine sulphate administration lasted 11 weeks, it was possible to administer DDS also orally to a maximum of 50 mgm. per day, without any untoward sign or symptom. At the time when the patient was really getting stabilised on DDS oral therapy under chloroquine protection, he discontinued.

In the second case (case No. 14) one of almost continuous reaction, the usual measures failed to control the reaction. He was put on chloroquine 200 mgm. twice a day and after 5 days there was complete subsidence of pain, although E.N.L. spots continued to occur. The dose was kept up at the same level and drug continued for a period of 7 weeks, because the reaction signs and symptoms showed a tendency to recur. At the end of this period, the patient said he was feeling "exhausted" and hence chloroquine was discontinued. After a break of 5 weeks, the reaction symptoms recurred and the patient was once more put back on chloroquine 200 mgm. b.d. After 5 weeks' treatment in the second course, there was considerable relief and then the patient was started on small doses of DDS orally, keeping him on a maintenance dose of 200 mgm. chloroquine per day. To this date, the patient is continuing sulphone in small doses, without the recurrence of lepra reaction. The E.N.L. spots keep coming in smaller numbers, and there is freedom from the agonising neuritis and arthritis.

3. *In Recurrent Reaction:* In 5 cases, chloroquine sulphate was administered on more than one occasion, when the reactions recurred —Case No. 1 had three courses, Case No. 2 two, Case No. 8 four courses and Case No. 9 two and Case No. 17 two. In cases Nos. 2 and 9, the results were good on both the occasions. In cases Nos. 1 and 8, the drug failed on one occasion in each and here relief was obtained by the intravenous injection of potassium antimony tartrate. In case No. 17, during the second course of treatment with chloroquine, the patient developed troublesome vomiting and hence the drug was discontinued.

Toxicity of Chloroquine

Toxic reactions attributable to the drug were encountered in 7 cases. In the order of frequency they were, vomiting in 4 cases, nausea in 1 case, transitory giddiness in one and psychosis in 1 case. In only one instance, vomiting was so severe as to necessitate withdrawal of the drug. In the rest, the vomiting was controlled either by withholding the drug for a day or two or with the administration of "Avomine".

One case (case 22) manifested signs of drug psychosis towards the end of chloroquine therapy. The patient had almost completely recovered from the reaction but exhibited unusual behaviour—he became apprehensive and disoriented: chloroquine was withdrawn and patient put on "Nevrovitamine 4-adults" and the symptoms passed off after about 10 days.

The general impression was that the toxic manifestations were of a mild nature, easily controllable.

General Comments

The mode of action of chloroquine in the lepra reaction syndrome is not clearly understood. PESTEL who considered lepra reaction a non-specific inflammatory process attributed the beneficial effect of chloroquine in this condition to its anti-inflammatory properties. MERKLEN contended that lepra reactions are not purely inflammatory since he had observed "the occurrence of the typical nodules of the disease". However, he confirmed the usefulness of Camoquin in this condition and considered it to be "more effective than K.thrombyl and less dangerous than phenyl-butazone".

Whatever may be the mode of action of chloroquine in lepra reaction the drug seems to have a definite place in the treatment of this condition. Although concurrent trials with potassium antimony tartrate have not been undertaken side by side with that of chloroquine, it can be said without reservation that the intravenous antimony therapy is quicker by far and more complete in controlling acute lepra reaction. This opinion is expressed from the experience gathered in the use of this preparation for the past several years. However, the great advantage with chloroquine sulphate is its easy administration, namely oral, which makes it very handy in the treatment of this complication in rural areas.

Something more important than just the treatment of acute lepra reaction with chloroquine is the assessment of the value of the drug in the treatment of recurrent, subacute, or chronic lepra reactions which make it impossible for the patient to catch up with his disease with adequate anti-leprosy treatment. Corticosteroids have been widely acclaimed as the drug of choice under these conditions. But the prohibitive cost of the drug and the none too favourable economic status of the leprosy patients necessitate the search for a cheaper, effective drug. Could this be chloroquine? From the results obtained in two cases it would be unwise to assess the efficiency of chloroquine in prolonged lepra reaction. However, the available evidence, though meagre, indicates its possible usefulness in the treatment of this condition. This deserves further investigation.

Summary

The usefulness of chloroquine sulphate in the treatment of lepra reaction is reported. The results indicate that the drug is effective in controlling acute lepra reaction arising in lepromatous leprosy. The easy administration of the drug by the oral route enhances its value as a therapeutic agent that is capable of wide application. Chloroquine seems to hold out a possibliity of controlling the "smouldering" lepra reaction and making the induction of sulphone therapy possible.

Acknowledgements

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References

1. THANGARAJ, R. H., *Leprosy Review*, **30,** 2, 1959, p. 106.
2. MERKLEN, F. P. and RIOU, M. R., *Presse Medicale*, **66,** 43, p. 984.
3. RAMU, G., *Journal of the Indian Medical Association*, **33** 4, p. 127.

EXAMINATION OF SMEARS FOR TUBERCLE BACILLI BY FLUORESCENCE MICROSCOPY

ELSE HOLST, D. A. MITCHISON, and S. RADHAKRISHNA
(*From the Tuberculosis Chemotherapy Centre*, Madras*)

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In underdeveloped countries, laboratory facilities for the bacteriological diagnosis of tuberculosis are, at present, very limited. Cultural methods are unlikely to be used on a large scale for many years to come. It is, therefore, important to investigate the most economical method of examining smears for tubercle bacilli. Fluorescence microscopy was introduced by Hagemann (1937) and has since been described by many authors, including Tanner (1941, 1948), Line and Shaughnessy (1941), Lempert (1944), Norman and Jelks (1945), Clegg and Foster-Carter (1946), Wilson (1952), Von Haebler and Murray (1954), and Needham (1957). The great advantage claimed for this method is that stained bacilli can be detected using a much lower magnification than with the usual Ziehl-Neelsen method. Considerable time is saved in examining smears and larger areas can be searched. The method has not been widely employed for two reasons. In the first place, the light source must be very bright and many of the optical systems described previously have only supplied sufficient light if the equipment was used in a darkened room. Secondly, some workers (Ritterhoff and Bowman, 1945; Kuster, 1939; Holm and Plum, 1943) consider that false positive results can be obtained, since some smears may contain small naturally fluorescent particles which can be confused with bacilli.

Equipment for fluorescence microscopy that can be used in normal daylight has been in use at the Tuberculosis Chemotherapy Centre, Madras, for over two years. When it was first introduced, a comparison between this method and the conventional Ziehl-Neelsen method was undertaken to test their relative sensitivities, and to see whether fluorescence microscopy yielded false positive results. The results of this comparison are described.

Methods

Fluorescence microscopy: Equipment.—The light source was a Zeiss multi-purpose microscope lamp III and lamp holder containing an Osram maximum pressure mercury vapour lamp, HBO74, operating from a mains connecting device. A heat-absorbing filter,

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and an exciter filter, BG12, were fitted to the microscope lamp. A mounted eyepiece barrier filter, OG5, was attached to the draw tube of the Olympus monocular microscope. The microscope was equipped with a Watson 16 mm. × 10 semi-apochromatic objective, a 4 mm. × 40 parachromatic objective for "uncovered specimens", a × 10 compensating eyepiece and a diamond objective marker. The usual parachromatic 16 mm. and 4 mm. objectives supplied as standard equipment for most microscopes could be used with only slightly less satisfactory results.

Staining (Lempert, 1944)

Auramine phenol.—Dissolve phenol crystals, 30 g. in one litre of distilled water. Warm to 40°C. and add auramine 0.3 g., shaking vigorously. Filter and store in a dark bottle.

Acid-alcohol.—Dissolve sodium chloride, 20 g. and concentrated hydrochloric acid, 20 c.c. in 500 c.c. distilled water. Add 74 O.P. alcohol, 1,500 c.c.

Potassium permanganate.—0.1% (w/v) in water.

Smears were heat fixed, stained for 6 minutes with auramine-phenol without heating, washed, decolourized with acid-alcohol for 2 minutes, washed and counter-stained with potassium permanganate for 30 seconds.

Ziehl-Neelsen microscopy.—The Ziehl-Neelsen procedure was a standard one (Mackie and McCartney, 1956), in which malachite green was used as a counter-stain. Smears were examined with a × 7 eyepiece and a 2 mm. × 100 oil-immersion objective.

Culture.—Sputum was treated for 15 minutes with about 4 times its volume of 4% sodium hydroxide. After centrifuging for 15 minutes, the supernatant was discarded. Distilled water was added to the deposit and after further centrifuging two 5 mm. loopfuls of the deposit were added, one to each of two slopes of Lowenstein-Jensen medium. The cultures were incubated for 8 to 9 weeks before being considered negative.

Sputum specimens.—A consecutive series of 1,383 sputum specimens that were cultured were examined by both smear methods. Of these, 981 (70.9%) were from patients who were not receiving chemotherapy. The remaining 402 (29.1%) were from patients during their first 6 months of chemotherapy, almost all with isoniazid and PAS.

Comparison of fluorescence and Ziehl-Neelsen microscopy.—Duplicate smears were made from each sputum specimen before treatment with sodium hydroxide. One was examined by fluorescence microscopy and the other after Ziehl-Neelsen staining by different technicians reading independently of each other. The result obtained by one method was recorded without knowledge of the result by the other method. The technicians who carried out the examinations had

some experience of Ziehl-Neelsen stains, but little of fluorescence microscopy. The results analysed are those obtained before checking by a senior member of the laboratory staff, and are, therefore, typical of the standards that reasonably competent technicians can obtain.

Positive smears were graded into three degrees of positivity, "scanty", "moderate", and "heavy". No particular attempt was made to ensure that these categories were identical for the two smear methods. A smear was called positive when it contained a minimum of 3 or 4 acid-fast bacilli of typical morphology.

Results

The smear and culture results on the 1,383 sputum specimens are given in the Table. Positive cultures were obtained from 655 (47.4%) of the specimens, and among these, 405 (29.3% of the total specimens) were positive by both smear methods, 36 (2.6%) by fluorescence microscopy only and 28 (2.0%) by Ziehl-Neelsen microscopy only. The remaining 186 culture-positive specimens were negative by both methods. Thus, fluorescence microscopy yielded a slightly larger number of positive smear results which were confirmed by culture, but the difference is not statistically significant.

TABLE

Smear and culture results on 1,383 *sputum specimens*

Culture result.	SMEAR RESULT:		SPECIMENS:	
	Fluorescence microscopy.	Ziehl-Neelsen microscopy.	Number.	Percentage.
Positive	Pos	Pos.	405	29.3
	Pos.	Neg.	36	2.6
	Neg.	Pos.	28	2.0
	Neg.	Neg.	186	13.4
Negative	Pos	Pos.	11	0.8
	Pos.	Neg.	4	0.3
	Neg.	Pos.	3	0.2
	Neg.	Neg.	681	49.3
Contaminated	...	...	29	2.1
Total	...	...	1,383	100.0

Among the 699 culture-negative specimens positive smears were found in 18 (1.3% of all specimens). Of these, the smears were positive by both methods in 11 (0.8%) instances, leaving 4 (0.3%)

which were positive by fluorescence microscopy only and 3 (0.2%) by Ziehl-Neelsen microscopy only. These results show that fluorescence microscopy did not yield smear-positive, culture-negative specimens (which might indicate false positive results) more frequently than did Ziehl-Neelsen microscopy.

From these figures, it will be seen that discrepant results with the two methods were more frequent in positive smears from culture-negative specimens (39% of 18 specimens) than from culture-positive specimens (14% of 469 specimens). This finding suggests that the excess with culture-negative specimens may be due to false positive smear results with one or both methods. However, the chance of a discrepant result was greater with a scanty positive than with a more heavily positive smear, and scanty positive smears were very much commoner in culture-negative than in culture-positive specimens. The effects of this association may be taken into account, and thus the possibility that there were false positive smear results with culture-negative specimens may be studied more precisely, in the following manner: Considering Ziehl-Neelsen microscopy first, there were 225 scanty positive smears in culture-*positive* specimens, and of these 27 (12.0%) were smear-positive by this method alone. Applying the same proportion to the 14 scanty positive smears in culture-*negative* specimens (all 14 of the Ziehl-Neelsen positive smears were scanty positive), the expected number of smears positive by Ziehl-Neelsen microscopy alone would have been 1.7 (i.e. 12.0% of 14); the number actually found was 3. A calculation on similar lines shows that the expected number of specimens yielding smears positive by fluorescence microscopy alone would be 2.4, whereas 4 were found. The difference between the numbers found and expected are small, and similar for both smear methods. Thus, there is again no evidence that false smear-positive results were being found among the culture-negative specimens by fluorescence microscopy.

Among sputa which yielded positive cultures, the percentages yielding negative, scanty, moderate and heavy smear gradings were 33.9, 34.4, 21.5 and 10.2 by Ziehl-Neelsen microscopy, and 32.7, 25.5, 29.5 and 12.4 by fluorescence microscopy. These data show a tendency for fluorescence microscopy to yield slightly higher gradings. Considering these specimens which were positive by only one of the smear methods, moderate gradings were assigned to 3 of the 36 smears positive by fluorescence microscopy only; and to 1 of the 28 smears positive by Ziehl-Neelsen microscopy only; the remainder were graded as scanty. Thus, taking into account the overall results of the grading of all culture-positive specimens, there was a similar distribution of smear positivity among those positive by only one smear method. These results from specimens proved positive by culture suggest that fluorescence microscopy is no more likely to yield false negative results than is Ziehl-Neelsen microscopy.

Discussion

Our comparison has shown that fluorescence microscopy reveals positive smears as often as does Ziehl-Neelsen microscopy. Moreover, there is no evidence that it yields any appreciable number of false positive or false negative results. The main advantage of fluorescence microscopy is a very great saving of time in the preparation and examination of smears. The area of the slide included in one field is about 50 times larger than with Ziehl-Neelsen microscopy, so that fewer fields need to be examined. Furthermore, the staining procedure is simpler, since no heating is required, and there is no need to use immersion oil during microscopy. In practice, the preparation, staining and examination of 100 smears is less than a day's work for one technician and their examination alone can easily be done in 2 hours. In comparison, the preparation and examination of the same number of smears takes at least twice as long if they are stained by the Ziehl-Neelsen method and examined with an oil-immersion lens. A second advantage is the saving in initial cost of equipment. A busy laboratory might require two microscopes for Ziehl-Neelsen microscopy but could examine the same number of smears by fluorescence microscopy with one. The cost of the additional equipment for the latter method is less than the cost of an additional microscope. The cost of replacing the mercury vapour lamps is much less than the salary of a technician.

Although fluorescence microscopy has the advantage of speed and cheapness, it requires more skill for its operation. The optical equipment needs careful adjustment to get maximum light transmission and it is, therefore, advisable to clamp the lamp holder and microscope permanently in position on the bench. If the electrical supply is interrupted the lamp cannot be relit for at least 3 hours after. Thus, it is necessary to have a spare lamp and to be able to change it easily. Skill is also required to distinguish with certainty acid-fast bacilli from other small naturally fluorescent particles present in some smears. When first using fluorescence microscopy, it is necessary to examine all small fluorescent objects seen both with the $\times$ 10 and $\times$ 40 objectives. With practice it becomes possible to distinguish bacilli with a fair degree of certainty under the $\times$ 10 objective only, so that almost all negative smears can be examined with this objective only. However, it is always necessary to confirm the bacillary morphology with the higher power when the smears are scantily positive. Finally, if any doubt remains, it is possible to ring individual suspicious objects with the diamond objective marker, then re-stain, over the fluorescence stain, by the Ziehl-Neelsen method, and examine with an oil-immersion lens. When smears are being examined by technicians, it is wise for a more senior member of the staff to check those that are judged to be positive. This only takes a few minutes each day, whereas checking of Ziehl-Neelsen

positives would take much longer.

Fluorescence microscopy can be recommended for the larger laboratory that examines at least 40 direct smears a day and where some supervision of the work of technicians is possible. Under these circumstances, it saves time and the initial cost of equipment. For the smaller laboratory it cannot be recommended so freely, since the need for greater skill in its use might lead to poor results.

Summary

The equipment and method for the examination of smears for tubercle bacilli by fluorescence microscopy is described. A comparison with the conventional Ziehl-Neelsen method on 1,383 routine sputum specimens which were also cultured showed that fluorescence microscopy yielded as many positive smears and had no tendency to produce false positive or false negative results. The method can be recommended for the larger laboratory as economical in time and initial expense.

References

CLEGG, J. W., and FOSTER-CARTER, A. F. (1946) *Brit. Jour. Tuberc.*, **40,** p. 98.
VON HAEBLER, T., and MURRAY, J. F. (1954) *S. Afr. Med. Jour.*, **28,** p. 45.
HAGEMANN, P. (1937) *Dtsch. Med. Wschr.*, **63,** p. 514.
HOLM, J., and PLUM, N. (1943) *Acta. Tuberc. Scand.*, **17,** p. 13.
KUSTER, H. (1939) *Dtsch. Med. Wschr.*, **65,** p. 92.
LEMPERT, H. (1944) *Lancet*, **247,** p. 818.
LIND, H. E., and SHAUGHNESSY, H. J. (1941) *Jour. Lab. Clin. Med.*, **27,** p. 531.
MACKIE, T. J., and MCCARTNEY (1956) "Handbook of Practical Bacteriology", London, p. 95.
NEEDHAM, G. M. (1957) *Proc. Mayo Clin.*, **32,** p. 1.
NORMAN, W. A., and JELKS, F. W. (1945) *Bull. Inst. Med. Lab. Tech.*, **11,** p. 37.
RITTERHOFF, R. J., and BOWMAN, M. G. (1945) *Amer. Jour. Clin. Path.*, **15,** p. 39. (Techn. Sect.)
TANNER, F. H. (1941) *Proc. Mayo Clin.*, **16,** p. 830.
TANNER, F. H. (1948) *Amer. Jour. Med. Technol.*, **14,** p. 83.
WILSON, H. M. (1952) *Amer. Rev. Tuberc.*, **65,** p. 709.

GRAVE RELAPSE OF A LEPROMATOUS LEPROSY PATIENT TREATED FOR SIX YEARS WITH THE SULPHONE J.51

R. CHAUSSINAND and N. BOURCART

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This note is about a lepromatous leprosy patient who had been presented as completely cured to the Société de Pathologie exotique in 1956[1].

It concerns M. G., a former administrator in the colonies who was born in Guadeloupe in 1896 and apparently contracted leprosy in Indochina where he lived from 1924 to 1946. The diagnosis was not made until 1948 in Paris when the patient had already reached an advanced lepromatous stage. M. G. was treated with the sulphone J.51 (Diatox argentique) from 1949 to 1955, in decreasing doses of 3 tablets of 50 mg. a day for the first 2 years, to 2 tablets for the next 2 years, to 1 tablet for the last 2 years. Treatment was finally stopped in 1955 as the patient was considered completely cured.

On 20th September 1957 M.G. had a relapse. Considering himself cured, he did not say he had had leprosy and his doctor thought he was dealing with an epidermomycosis. The patient was then treated for 13 months for trophic disorders of the hands and feet of vascular origin. On 7th January 1959 M.G. had a new cutaneous evolutive reaction. Histopathological examination of biopsies taken from the hands gave the following result:

The epidermis, in localised patches lightly involved in hypertrophy of the prickle layer, was hypokeratotic and thinned out into diminishing interpapular prolongations, and separated by a thin band of the fibrous dermis from a granuloma with multi-lobular foreign bodies with histiocytes and plasmocytes. There were asteroid bodies. There was neither angiomatosis, nor any change in the capillary permeability.

There were very numerous Hansen's bacilli in the vacuoles and the histiocytes. (Z.N.)

Lepromatous leprosy of the kind which sometimes shows gigantocytes (Dr. Destombes).

M.G. was sent to us on 24th January.

In the clinical examination, we observed numerous cutaneous lepromatous lesions, purplish-blue in colour, more or less infiltrated, scattered over all the body, except for the chest, and the face appeared somewhat leonine. According to the patient, the cutaneous lesions were more considerable than those which had occurred before undergoing treatment with the sulphone J.51. There was no report

of polyneuritic troubles. Bacteriological examinations of the skin and of the nasal mucus showed the presence of very numerous homogenous Hansen's bacilli, partially grouped in globi. The Mitsuda reaction was negative. The case presented advanced lepromatous leprosy.

M.G. was then treated with diamino-diphenylsulphone (DDS) in a moderate dosage, slowly increasing, which did not exceed the maximum dose of 2 mg./kg. He reacted favourably to treatment without the least disturbance being shown.

This observation is instructive from several points of view:

It is clear first of all that many practising doctors experience great difficulties in diagnosing leprosy, and yet this infection is easy to recognise. In effect, in benign leprosy with few bacilli, certain disturbances, more or less pronounced, of the superficial sensation one always notes as far as the lesion of the skin is concerned. It is true that in the early lesions these disturbances can be minimal. However, unfortunately it is rare for patients to consult a doctor at this stage of the infection. Eventually, hypertrophy of a nervous trunk in the limbs and the local anaesthesia of neuritic origin can also facilitate the clinical diagnosis. With regard to malignant lepromatous leprosy, disturbances of the superficial skin sensation in relation to the lesions are sometimes absent and occasionally unimportant. However, bacteriological examination always reveals itself very clearly positive in the lesions of the skin. Nasal mucus also contains very numerous Hansen's bacilli, partially grouped in globi, except with certain patients whose lepromatous evolution is more or less recent.

To diagnose leprosy, it is sufficient minutely to seek out perversion, lessening or loss of sensation to touch, heat, cold, and pain with regard to skin lesions, and to take a little fragment of a lesion for bacteriological examination. At the present time, when cultural and economic ties between France and Overseas assume more and more importance it is essential that every practising doctor should be able to recognise leprosy.

Moreover, it stands out from this observation that treatment by the sulphone J.51 was clearly insufficient. That is not at all surprising since Floch, working on the levels of sulphone in the blood, showed that 200 mg. of J.51 sulphone is about the equivalent of 50 mg. of diamino-diphenylsulphone (DDS)[3]. M.G. would therefore only have received the therapeutic equivalent of about 39 mg. of DDS a day for 2 years, then 26 mg. for the next 2 years, and then 13 mg. for the last 2 years. It is evident that no leprologist would dare to attempt the treatment of leprosy by administering such small doses of DDS.

The slight toxicity claimed for the sulphone J.51 is entirely due to the small quantity of DDS liberated *in vivo* which passes into the blood system[4]. To obtain a therapeutic action comparable to that

of the sulphone J.51 it is sufficient to administer a dose 4 times more feeble of DDS and in that case the small toxicity of the 2 drugs is identical. Besides, treatment of leprosy by the sulphone J.51 is much more costly than the standard treatment by DDS. There is therefore no advantage to be gained in using this derivative of DDS in the therapy of leprosy.

It is however indisputable that the state of M.G. was improved by the sulphone J.51. This shows that DDS works in very small doses and that the use of that dosage, which one of us has advocated since 1951, is perfectly justifiable[2]. The dosage which gives us complete satisfaction clinically and bacteriologically is the following:

We always start treatment with the oral administration daily of 25 mg. of DDS and only increase this dose very slowly, in steps of 25 mg. In practice, we only arrive gradually at the maximum dose of 2 mg./kg. after 5 months of treatment with patients with benign leprosy and only towards the 10th month with patients with the malignant lepromatous type who risk being disturbed by complications with doses too strong or progressing too rapidly.

Although with the use of weak doses of DDS increased very slowly anaemia only occurs in exceptional cases, we use tablets of 100 mg. DDS containing 200 mg. of protoxalate of iron. These tablets can be broken into 4 equal parts, giving doses of 25, 50 and 75 mg.

As the treatment of leprosy patients must be continued over several years it is recommended that the drug should be administered only 6 days out of 7 and that a week's rest should be prescribed regularly after 3 weeks of treatment to avoid an eventual accumulation of DDS in the body. These halts of short duration should not cause any inconvenience.

The oral administration of DDS daily according to the dosage given above is without any doubt the best treatment for leprosy, probably because it causes blood sulphone levels relatively weak, yet steady and constant enough.

Many leprologists still actually use DDS in doses too strong and progressing too rapidly. This increased dosage not only does not bring any more spectacular improvement than the one we advise but on the contrary brings about the frequent occurrence of complications, more or less serious (anaemia, reaction).

Certain authors fear that the treatment by DDS in small doses progressing slowly could bring about a resistance to sulphone in the Hansen's bacillus. This fear has no foundation, since from 1948 no characteristic case of resistance to sulphones can be found among the hundreds of thousands of patients who undergo, more or less regularly, treatment by DDS. On this subject also the observation of M.G. is of great interest. In effect, this patient followed a sulphone treatment for 6 years, actually equivalent to small and decreasing

doses of DDS (39 mg. to 13 mg. a day). In spite of this dosage, which should have induced the occurrence of resistance to sulphones, the introduction of a new treatment by weak doses of DDS still produced in a short time a remarkable improvement in the cutaneous lesions caused by a serious lepromatous relapse.

References

1. BASSET, A. Resultats eloignés du traitement de la lèpre par la sulfone J.51. *Bull. Soc. Path. Exotique*, 1956, **49,** 593.
2. CHAUSSINAND, R. Thérapeutique de la lèpre. *Rev. Practicien*, 1954, **21,** 1955; Condense de leprologie à l'usage du médecin praticien. *Sem. Hop. Paris*, 154, **79,** 4405; La Lèpre, 2nd edit., *Expansion Scientifique Française, edit., Paris.*
3. FLOCH, H. and GELARD, A. M. La sulfone J.51 en thérapeutique antilepreuse. *Bull. Soc. Path. exotique*, 1955, **48,** 133.
4. RIST, N., BOYER, F., SAVIARD, M. and HAMON, V. Sur le mode d'action d'une sulfone thymolée argentique. *Rev. Tuberc.*, 1954, **18,** 1407.

THE PROBLEM OF THE NATURE AND OF THE SIGNIFICANCE OF THE MITSUDA REACTION TO LEPROMIN

R. CHAUSSINAND
(*Institut Pasteur, Paris; this paper is reprinted in English translation approved by the author, by kind permission of the Editor, Ann. de l'Institut Pasteur. The article appeared* August, 1959, **97**, pp. 125–134)

The interpretation of the nature and the significance of the reaction to lepromin becomes more and more difficult.

Lepromin is a filtered and autoclaved suspension of 1 g. of lepromatous nodules, finely ground, in 30 ml. of physiological saline, 0.5% carbolised. This antigen contains Hansen's bacilli heatkilled and some tissue debris. The Mitsuda reaction is found by injecting 0.1 ml. of lepromin intradermally. The result is positive when an erythematous infiltration, which reaches its height at the end of 3 to 4 weeks, forms at the point of the injection. Small infiltrations of less than 3 mm. in diameter are considered as doubtful. In strongly positive cases, the nodular infiltration can ulcerate. Towards the 30th day the histological aspect of the reaction is tuberculoid in type.

Twenty years ago it was considered that sensitivity to lepromin was always a sign of a relative state of immunity against leprosy. This opinion was based on the following premises:

Patients with tuberculoid leprosy, with few bacilli, usually react strongly to the Mitsuda reaction, while leprosy patients of the malignant lepromatous kind, whose body is rapidly invaded by Hansen's bacilli, are insensitive to lepromin.

Moreover, benign leprosy never changes to the malignant type, so long as the patient reacts to lepromin.

Finally, epidemiological enquiries seem to show that those with a positive Mitsuda reaction contract leprosy in contact with contagious patients less frequently than those insensitive to lepromin.

It is admitted then quite reasonably that sensitivity to lepromin was provoked by the impregnation or by the infection of the body by the Hansen's bacillus and that it was witness of the presence of a relative state of immunity, shown in a marked resistance of the tissues to the multiplication and invasion of the pathogenic agent.

Actually, sensitivity to lepromin, owing to the attack on the body by the leprosy bacillus, keeps without any doubt all its prognostic value; clinical and immunological studies amply show this. A positive Mitsuda reaction, determined by a primary leprosy infection, remains the sign of an immuno-allergic state which is expressed in a resistance of the body not only to superinfections but also to the primary infection, by arresting evolution to the malignant type. Immuno-allergy in leprosy is therefore different from that observed in

tuberculosis which protects the body against further infections, but has no action on the evolution of the primary infection.

The immuno-allergic state in leprosy also shows other special features. Thus in a country where leprosy is strongly endemic the Mitsuda reaction is rarely positive in the first two years of life. It is only from the age of three that the number of allergic subjects gradually increases with age. Souza Campos seeks to explain this by a theory based on the existence of a rare, infantile form of tuberculoid leprosy which would cure itself completely without the help of any therapy after the ulceration and scarring of the cutaneous lesions[15]. This author thinks it is possible that the child would benefit from an immunity transmitted by its mother during intra-uterine life.

We have never had the opportunity of observing cases of this early abortive leprosy, but the study of the cases published by Souza Lima, Souza Campos, and Pessôa Mendes[16, 14] confirms that the majority of children suffering from this special kind of tuberculoid leprosy have lepromatous mothers. Also it seems improbable to us that these mothers whose bodies show no resistance to the invasion of the leprosy bacillus should be able to transmit to their children a relative immunity which they themselves do not have. We consider moreover that the rarity of sensitivity to lepromin in children of less than 3 years could be due in part to the long incubation of leprosy which seems to be on an average of 2 to 3 years.

Another point is that this immuno-allergic state which can be discovered by the Mitsuda reaction is often varying in its intensity and can even disappear. At the time when chaulmoogra oil was the only remedy for leprosy we were able to note on many occasions that patients with benign leprosy who reacted at first, often strongly, to lepromin would become anergic. (At the present time, the treatment by sulphones, if it is regularly continued, prevents always the malignant evolution and that even in the originally anergic leprosy patients.) The appearance of this insensitivity to lepromin did not show itself in a weakening of the general condition nor in a clinical deterioration (sometimes the cutaneous and neuritic lesions improved) nor even in an increase in the number of bacilli in the lesions. It was only later, at the end of several months and sometimes after many years, that this benign anergic leprosy changed quickly into malignant leprosy. The anergy then is not caused by a strong increase in bacilli in the lesions as some authors claim, as it precedes the invasion of the body by the pathogenic agent. Immuno-allergy in leprosy does not depend on the kind of infection, on the contrary it is the factor that determines the benign or malignant development of the disease. This confirmation is extremely interesting since it provides an important proof of the immunological and prognostic value of the Mitsuda test.

Rotberg[17] believes that sensitivity to lepromin can only be

produced in a body with a special power of resistance, the natural N factor. This factor in the presence of leprosy or tuberculosis infection or of BCG vaccination would bring about sensitivity to lepromin, while organisms without this N factor would be incapable of reacting to this antigen.

It is futile to say that factors which bring about the appearance and disappearance of allergy in leprosy are not known. Yet, every body has the innate faculty to react to infections, but seemingly in a variable manner according to the race, the family, the age, the sex, and the physiological individuality. In leprosy, anergy does not seem to depend on the absence of a hypothetical N factor, but rather on metabolic phenomena capable of depriving the body of the faculty to react to the infection, either temporarily or for good.

So the result of our research done at Saigon showed that leprosy has a more serious development in the male sex. Moreover, it seems that puberty brings about an appreciable increase in the number of malignant cases among boys while it diminishes the risk of malignant development among girls. This resistance of the female body to the bacillary dissemination and invasion gives way in a marked manner between 20 and 30 years, an active period concerned with gestation. Clinical observations indicate moreover that pregnancy and confinement often cause an increase in the development of leprosy. Besides, this resistance to infection weakens among the Vietnamese and the Chinese between 40 and 50 years, that is to say during the menopause. In our opinion, the original anergy and the loss of the immuno-allergic state in leprosy could be the result of modifications in the metabolism, partly determined by physiological changes or by pathological disturbances of the endocrine secretions[4, 5].

The immunological and prognostic value of the Mitsuda reaction owing to the previous attack on the body by the leprosy bacillus remains indisputable. However, it is recognised now that sensitivity to lepromin can be induced, not only by a primary leprosy infection but also by tuberculosis or vaccination by BCG and also, according to certain authors, by repeated intradermal injection of lepromin, that is to say of heat-killed Hansen's bacilli. In these cases, may the Mitsuda reaction be considered as the sign of an immuno-allergic state equal in value to that determined by a primary leprosy infection? It is impossible to reply to this question with certainty.

As regards tuberculosis, a mycobacterial infection related to leprosy as the haemagglutination of Middlebrook-Dubos[9, 18] showed, we are convinced that a Mitsuda reaction, due to the impregnation or to the infection by the Koch bacillus, is equally the sign of a certain state of resistance in the body to the Hansen's bacillus. All the leprologists who have studied during epidemiological research the theory of antagonism between tuberculosis and leprosy which we put forward in 1944[1] have come to conclusions in favour of this

theory. In effect, leprosy disappears gradually wherever tuberculosis greatly spreads and it can only flourish in those parts little or recently attacked by tuberculosis. But has this para-allergy brought about by the Koch bacillus the same immunological significance as the allergy released by a leprosy infection? In fact we do not know. It is however possible that the eventual relative immunity caused by the tuberculosis infection is more feeble than that produced by the pathogenic agent of leprosy, since the Koch bacillus is an acid-resistant germ of a similar kind, yet different even so from the Hansen's bacillus. New epidemiological, clinical, and immunological studies will doubtless bring light on this complex subject.

Vaccination by BCG determines in a very large percentage the conversion of the Mitsuda reaction among people free from leprosy and tuberculosis. For, if tuberculosis brings about a certain state of defence in the body against leprosy, vaccination by BCG should have the same effect, but seemingly to a lesser degree, BCG being a germ of bovine origin and of very small virulence which can only maintain itself in a body for a relatively short time[7].

If it should come about that the para-allergy set up by BCG was really the sign of a certain state of resistance to the Hansen's bacillus, the problem of the prophylaxis of leprosy would be very largely solved. But although numerous publications on this subject have given favourable results, new experiments should be undertaken in the course of which we shall see how the control group not vaccinated compares with the vaccinated group as regards exposure to the infection, age, sex, and notably the previous clinical examination. Moreover, periodic revaccinations seem essential as occurs in premunition against tuberculosis.

It seems to us that the following experiment, carried out with children resistant to lepromin and to strong doses of tuberculin, could furnish useful indications of the eventual preventive action of BCG against leprosy.

Groups of controls and of those to be vaccinated would be formed according to the recommendations given above. Children to be vaccinated would receive 100 mg. of BCG orally and would be revaccinated every year by the same method. Finally, those vaccinated and the controls would undergo every year a thorough clinical examination.

The interpretation of the nature of the Mitsuda reaction obtained after repeated injections of lepromin is very tricky. One must at once state that trials in man have been carried out in a way open to criticism. In effect, this experiment had been carried out in the first place on the children of leprosy patients and then on people apparently healthy, living in regions where leprosy and tuberculosis were more or less endemic[10, 11]. It is therefore impossible to know if certain of these Mitsuda reactions had been provoked by

the repeated injection of lepromin or by unknown latent infections due to Hansen's bacillus or Koch's bacillus. It would seem better to carry out this experiment in countries where leprosy has been unknown for many years. The subjects of this research should be insensitive not only to lepromin but also to strong doses of tuberculin. Moreover, these people should be chosen from regions not exposed to the tuberculosis infection. Finally, among those who become sensitive to lepromin only those remaining negative to strong doses of tuberculin should be taken into consideration.

Can we claim, at least theoretically, that in the absence of all leprosy or tuberculosis infection the repeated injection of lepromin can assure a certain state of resistance to Hansen's bacillus? The study of immuno-allergy in tuberculosis could throw some light on the subject.

Thus, in a guinea-pig, after a subcutaneous injection of 0.1 mg. of virulent Koch bacillus, the superinfections produce after about 10 days ulcerated lesions of developing tuberculosis. However, as early as the appearance of sensitivity to tuberculin, which takes place about the 25th day, lesions of reinfection appear at shorter and shorter intervals. About 40 days after the primary inoculation if the animal is superinfected intradermally with a sufficient dose of bacilli the phenomenon of Koch appears.

In fact, one or two days after this superinfection one notes the formation of a necrosing ecchymotic infiltration at the point of injection. The injected bacilli are generally eliminated with the scab, and there is no glandular lesion. The superinfection is arrested while the primary infection follows its normal fatal evolution. The Koch phenomenon consists of two superimposed reactions, one of hypersensitivity characterised by the ecchymotic and necrotic changes, the other of immunity, expressed by the arrest of the tuberculosis superinfection.

Hypersensitivity can be discovered and even provoked just as well with living bacilli as with dead bacilli. There is an antigenic sensitivity, analogous to tuberculin sensitivity. On the contrary, the state of resistance to superinfections, or premunition can only be obtained after a primary infection, that is to say after an inoculation of living Koch bacilli. So the normal guinea-pig, previously injected with dead bacilli, will become allergic to tuberculin and present a typical Koch phenomenon after a second injection of dead bacilli, given about 40 days later. However, in spite of the indisputable Koch phenomenon, the animal will not be immune since an inoculation of living bacilli will produce developing tuberculosis. It appears then from one point of view that the allergic test is not the sign of a state of immunity but only of an acquired sensitivity, and from another that the immunity of superinfection or premunition can only be induced by the presence of living bacilli in the body. More-

over, if the superinfection is carried out at a feeble dosage, only the phenomenon of resistance will appear. A state refractory to superinfection can therefore be produced without being preceded by local or general signs of hypersensitivity.

It is possible to conclude that allergy and immunity represent two reactional capacities, which, even if they are habitually joined and superimposed, remain separate, whether in spontaneous conditions of infectious pathology or in experiment (Gastinel).

It should also be stated that in 1944 we brought about for tuberculosis a reaction similar to the Mitsuda one, from which came the BCG test[2, 3, 6]. The antigen was composed of a suspension of virulent Koch bacilli, heat-killed, in 0.5% carbolised physiological saline. The number of germs in the antigen was approximately equal to the number of Hansen's bacilli contained in lepromin. We were able to show with tuberculous patients that the reaction provoked by that antigen was macroscopically and histologically similar to that of Mitsuda. Moreover, the phenomena of hypersensitivity were more marked and their evolution was more rapid. In effect, the height of the reaction, which showed itself by ulceration, was obtained as early as at 1 or 2 weeks.

Now we had to prove on guinea-pigs that this reaction similar to that of Mitsuda in leprosy was not always accompanied by an immune state, since animals inoculated with dead bacilli and sensitized to this reaction, died after a later inoculation of virulent Koch bacilli. On the contrary, the guinea-pigs with a positive reaction after a primary infection of tuberculosis resisted superinfections. In tuberculosis the reaction to the antigen prepared with heat-killed Koch bacilli is only, like the Koch phenomenon, a hypersensitivity reaction. It only acquires an immunological significance in a body previously impregnated with living germs.

The nature of the sensitivity to lepromin of a body impregnated or infected by Hansen's bacillus seems to be close to that of the Koch phenomenon and to the reaction that we have suggested for tuberculosis. In effect, the Mitsuda reaction is equally shown by a hypersensitivity, accompanied by an immune state. However, the signs of hypersensitivity are less pronounced, while the relative immunity shows itself more powerful since it hinders the malignant evolution of the primary infection. Nevertheless, this immuno-allergy can diminish in intensity and even disappear completely. Moreover, the Mitsuda reaction usually begins 1 or 2 days after the injection of the antigen (early reaction of Fernandez), but its final development is less acute and of longer duration. Finally, to the leprominic allergy properly so called is joined a foreign body reaction. The antigen contains in fact tissue debris and Lopes de Faria showed in 1953 that an injection of 0.1 ml. of a suspension of normal cutaneous tissue, crushed and filtered, in physiological saline

(1:20) could provoke a weak reaction, but macroscopically and histologically identical to that of Mitsuda[12], in lepromin sensitive subjects. It is also known that the bacillary antigen of Fernandez, which no longer contains tissue debris, in practice gives late Mitsuda reactions clearly more feeble than lepromin prepared according to the Hayashi-Wade technique.

It appears from the study of immuno-allergy in tuberculosis, a mycobacterial infection related to leprosy, that it is very unlikely that the repeated injection of lepromin, that is to say of dead Hansen's bacilli, could bring about the appearance of relative immunity. This proceeding could more or less determine a hypersensitivity, bound to a foreign body reaction. Besides, the clinical and typical histological aspect of a Mitsuda reaction is not always witness of an immune state.

Thus, Convit, Lowe, and their collaborators could note that intradermal BCG vaccination brought about in 11 to 41% of lepromatous patients a slight sensitivity to lepromin[8, 13]. Now it seems improbable that this sensitivity could be interpreted as the sign of an immune state. One will hardly believe that a BCG injection can cause such an immunological change in the body of patients very strongly bacilliferous and anergic to the Hansen's bacillus, since one knows that a lepromatous patient, ulteriorly impregnated or infected by the Koch's bacillus, always remains insensitive to lepromin. Lowe has also shown that these weakly positive Mitsuda reactions noted in lepromatous cases vaccinated with BCG are of short duration and are not followed by clinical or bacteriological improvement in spite of continued treatment. It can only be in these cases a transitory cutaneous sensitivity without immunological significance[5].

From this it seems that sensitivity to lepromin can be considered as an allergic phenomenon, linked to a foreign body reaction. It will not be *ipso facto* witness of an immune state and will only assume an immunological value with subjects already impregnated by living Hansen's bacilli. The present theory, which is to interpret the early reaction of Fernandez as a phenomenon of hypersensitivity and the late Mitsuda reaction as a test of immunity, will have to be revised.

Tuberculosis and leprosy are related mycobacterial infections and it is therefore possible that the para-allergy to the Hansen's bacillus of subjects attacked by tuberculosis or BCG vaccinated is also bound up with a certain degree of resistance in the body to the leprosy infection. However, only clinical observation will finally give us grounds to affirm this.

As regards the allergic Mitsuda reaction, provoked by the repeated injection of lepromin, it is apparent that it only represents a cutaneous sensitivity without immunological significance.

Summary

The author attempts to define the nature and significance of the Mitsuda reaction by studying the clinical and immunological data on leprosy and tuberculosis, which are related mycobacterial infections, as evidenced by the Middlebrook-Dubos haemagglutination reaction.

The author considers sensitivity to lepromin as an allergic phenomenon, associated with a foreign body reaction. This sensitivity does not necessarily prove immunity, and should only have immunological significance in individuals already contaminated by living Hansen bacilli. The current theory, considering the early Fernandez reaction as a sign of sensitization and the late Mitsuda reaction as an immunity test, should then be revised. However, the paraallergy to Hansen bacilli observed in tuberculous or BCG-vaccinated individuals might be related to a certain degree of resistance to leprosy infection. Only clinical study will allow a conclusion.

Mitsuda allergic reaction induced by repeated injections of lepromin (i.e. dead Hansen bacilli) seems to be due exclusively to cutaneous sensitization without immunological significance.

References

1. CHAUSSINAND, R., *Rev. Med. Franc. E.-O.*, 1944, **22,** 667; *Int. J. Lep.*, 1948, **16,** 431 and 1957, **25,** 365.
2. CHAUSSINAND, R., *Rev. Med. Franc. E.-O.*, 1944, **22,** 799; *Ann. Inst. Pasteur*, 1947, **73,** 811.
3. CHAUSSINAND, R., *Rev. Med. Franc. E.-O.*, 1944, **22,** 803; *Ann. Inst. Pasteur*, 1947, **73,** 814.
4. CHAUSSINAND, R., *Int. J. Lep.*, 1947, **15,** 406.
5. CHAUSSINAND, R., *La Lèpre, 2e edit.* Expansion scientifique française, Paris, 1955.
6. CHAUSSINAND, R., *Rev. Tub.*, 1957, **21,** 530.
7. CHAUSSINAND, R. (in collaboration with M. VIETTE). Prophylaxie et thérapeutique de la lepre, G. Doin, Paris, 1958.
8. CONVIT, J., ROSSI, E., RODRIGUEZ, F. C., and CONTRERAS, R., *Int. J. Lep.*, 1952, **20,** 347.
9. GERNEZ-RIEUX, C., MONTESTRUC, E., and TACQUET, A., *Bull. Acad. Nat. Med.*, 1952, **136,** 375.
10. IGNACIO, J. L., PALAFOX, C. A., and JOSE, F. A., *Jr.*, *Int. J. Lep.*, 1955, **23,** 259.
11. LARA, C. B., *Month. Bull. Bur. Hlth. Manila*, 1939, **19,** 15; *Int. J. Lep.*, 1940, **8,** 15.
12. LOPES DE FARIA, J., Contribuição ao conhecimento da natureza da reação de Mitsuda. Departamento de Imprensa Nacional, Rio de Janeiro, 1953.
13. LOWE, J., and MACNULTY, *Int. J. Lep.*, 1953, **21,** 173.
14. PESSÔA MENDES, J. Tese de concurso à Livre-Docência, 1956, Pôrto Alegre.
15. SOUZA CAMPOS, N., *Rev. Bras. Lep.*, 1937, **5,** 99.
16. SOUZA-LIMA, L. DE, and SOUZA CAMPOS, N. Lepra tuberculoide, Editora Renascença, Sâo-Paulo, 1947.
17. ROTBERG, A., VIe Congrès, *Int. Lep.*, 1953, 656.
18. VIETTE, M., *Ann. Inst. Pasteur*, 1954, **86,** 76.

ABSTRACTS

(On melanosis and hypermelanosis; cytoplasm structure in *M. leprae;* elongation of *M. lepraemurium* in a cell-free medium; initiation of a trial of BCG vaccine for leprosy; inoculation of golden hamsters producing histiocytic granulomatous leprosy-like lesions; preliminary report of the effect of DDS on malaria in N. Nigeria)

Melanosis, a Peculiar and Rare Dermatosis seen in the African of Mashonaland. M. GELFAND. The Central African J. of Med., **5**, 11; Nov. 1959, pp. 595–598: 5 illustrations.

Dr. Gelfand records an important observation of his of the occurrence of black, oval, or circular macules of hyperpigmentation or melanosis in adult Shona of both sexes. He describes 3 cases, with clear photographs. The macule has an average diameter of 2 cm. and a few or many appear widely on the body, the trunk being the most typical site. The only difference between macule and healthy skin is its deeper black colour, and skin biopsy shows no apparent abnormality except for the excess of melanin pigment in the skin. The patches seem to be permanent, though the patients say that they fade away and are followed by others. In addition to the apparently more permanent lesions, the patient may describe a much more transitory eruption consisting of reddish papules which fade after several days only to be followed later by the black lesions at a fresh site. Most cases also have attacks of abdominal pains of a few days duration which may be so severe as to end up in laparotomy. This pain may be felt in any part of the abdomen and end up in vomiting. The prognosis as to life appears to be excellent. Gelfand has occasionally seen cases with temporary non-recurring black circular macules as described by M. Rose (1958) in Med. Proceedings, Baragwanath Hosp., Johannesburg **4**, 314, in which the skin is lustreless and sooty in appearance and after 3 to 4 days the pigmented area begins to shrink and peel, leaving a paler skin underneath.

In the illustrative cases described by Dr. Gelfand, some further interesting points emerge:—(*a*) In the first patient, a male, there were crops of melanotic macules all over the body. When they were young, there was *itching* in them. Before the macules appeared there would invariably be *severe pains in the abdomen and chest*, immediately followed by pink papules, which itched, could appear anywhere, and disappear after about 3 weeks. The pain could be independent of the papules. There was no fever at any time, and he was fit and well-nourished. Laboratory investigations were negative. Skin biopsy showed only *a diffuse fibrosis in the corium*. No urobilins or porphyrins in the urine. A second skin biopsy showed *slight hyperkeratosis*, and *perivascular accumulations of pigment* in the cutis, but no significant lesion. (*b*) The second patient was an adult African Shona female, aet. 26 years. Since 1951 she complained of lower abdominal and vague upper abdominal pain for which no cause could be found. There was occasional vomiting. In 1955 black circular hypermelanotic

macules first appeared on the lower abdomen and continued to appear there until June, 1958, when they also turned up on her legs. The early macules were preceded by localised itching, and the early macules were first of reddish colour, but very soon became black. Latterly pain instead of an itch has preceded the appearance of a macule, and the lower abdominal pains have become more severe and intermittent, with no fixed time relationship to anything. All examinations were negative, and the patient continues to look fit and well, except for the black circular patches on the skin, which remain unaltered. (*c*) The third patient was an African male aged about 50 years. In 1958 he first began to complain of painful ulcers on his tongue and gums, and at the same time dark circular patches appeared on his arms, chest, and right leg. There was an occasional rise of temperature to 99°F. (37.3 C.), and he took 1 aspirin tablet at the beginning. The temperature soon returned to normal and remained so. His B.P. was 170/100. After several days the black patches began to crack and the dead skin peeled off in tiny fragments, leaving a hypopigmented but otherwise healthy-looking skin underneath. Dr. M. Rose has recorded a similar case to this, in which the rash peels after a while, and attributes it to the taking of phenolphthalein previously as a purgative. The rash in the first 2 cases is entirely different and requires explanation. (In connection with Dr. Gelfand's paper, see letters by B. NICHOLSON and S. G. BROWNE in *Leprosy Review*, **30**, 4, and **31**, 1, of Oct. 1959 and Jan. 1960 respectively; also the two Abstracts which follow here immediately. EDITOR).

A Hypermelanotic Rash Complicating Sulphone Therapy: S. G. BROWNE. Trans. Roy. Soc. of Trop. Med. & Hyg., **53**, 6; Nov. 1959, pp. 495–505.

The author describes and discusses a little-recognised complication of sulphone therapy in leprosy, namely hypermelanotic macules in the skin and mucosae of leprosy patients, who were all deeply-pigmented Bantu of the Belgian Congo. Apart from drug therapy, no cases were observed. Apart from sulphones, only 2 cases were observed, 1 with sulphaguanidine and 1 with sulphathiazole. Bantu are known to respond excessively to stimuli causing hyperpigmentation, much as they do to factors causing a fibrotic and keloid response. In all, 160 cases of the hypermelanotic macules were observed in a population of 43,035 persons, of whom 5,349 were under treatment for leprosy. Rounded, black, or purplish-black macules appeared suddenly in the skin or mucosae, typically 1 cm. in diameter, but varying from 0.5 cm. to a less well-defined diffuse larger type. Crops of macules may appear over months or years. After sulphone therapy ceases, the macules tend to disappear in 9 to 18 months. Scratching may modify the course and even introduce

areas of light blue colouration. There are a few cases of acute severe onset, with irritation, vesicles, bullae, and oedema. Sometimes there is desquamation. There has been no family incidence. The sulphone therapy was either Dapsone with iron by mouth, or 50% Solapsone by injection, or Dapsone in 25% suspension in hydnocarpus oil. The incidence of the rash was a bit lower with the oral than the injection treatment, but all three methods could cause it. The time before the rash appeared under sulphones varied considerably, average 18 months to 2 years. Distribution of macules on the body was apparently haphazard, even in relation to the form of leprosy and to the existence of a lesion or not in the site of appearance of the macules, nor is there any relation to the occurence or speed of the clinical arrest of the leprosy. The fading out of the hypermelanotic macules seems to be independent of the form of sulphone given. Of the 160 patients, 48 had symptoms which could be attributed to the macules, mostly moderate or severe skin irritation. A few had pain which interfered with sleep, or a generalized pruritis, or a local burning sensation with objective heat. Histologically in the macules there is remarkably little change. There is an increase in melanophores and pigment, and the suggestion is of a disturbance in the functional activity of the melanoblasts, perhaps a direct toxic action by DDS on areas of sensitive melanoblasts, with consequent alteration in the mechanism of formation or storage or transport of melanin.

Hypermelanotic Rash Associated with Sulphonamide Therapy: S. G. BROWNE. Brit. Med. J., Feb. 27, 1960, p. 621.

He describes an eruption identical to that observed by him in sulphone therapy, in 2 cases in the Belgian Congo where sulphaguanidine had been taken, in the one for diarrhoea and in the other for pustular dermatitis. There was widespread skin irritation, small bullae, macules coming out in crops which were hypermelanotic and faded slowly.

Cytoplasm Structure in Mycobacterium leprae. E. M. BRIEGER, AUDREY M. GLAUERT, and JENNIFER M. ALLEN. Experimental Cell Research, **18**, 1959, pp. 418–421. 1 plate.

The authors earlier had noted laminated structures in electron micrographs of *Mycobacterium avium* but could not identify them nor assign a function to them. These round or oval bodies lay in the cytoplasm and resembled the unidentified bodies seen in *B. subtilis* by Ryter and colleagues. Later Shinohara and colleagues described laminated structures in avian tubercle bacilli and thought that they might be related to the nuclear apparatus and to mitochondria. Later Glauert and Hopwood found a remarkable system of intracytoplasmic membranes in study of thin sections of hyphae of *Streptomyces coelicolor*, which seemed to be continuous with the plasma

membrane. The present authors have now seen systems of membranes in the cytoplasm of human leprosy bacilli obtained from Africa (fixed in a standard buffered osmium tetroxide solution in Africa and then stored in 70% alcohol until they were embedded in n-butyl methacrylate in Cambridge many weeks later. Good sections were obtained by a thin-sectioning microtome designed by A. F. Huxley). These membranes are sometimes seen in parallel arrangement, and sometimes form stacks at the point of cell division of the mycobacterium. The membranes are often connected with the plasma membrane, which appears as a "double" structure made up of 2 dense layers, each about 3 mμ thick, separated by a less dense layer about 4 mμ thick. The membranes in the cytoplasm are about the same thickness, and sometimes they form structures which resemble those noted earlier in avian tubercle bacilli. These peculiar cytoplasmic membranes seem common to *Streptomyces* and *Mycobacterium*, but it is not known whether they are peculiar to them, nor whether they appear only at certain stages of development. It may be that their presence in leprosy bacilli is an indication of growth. There are morphological similarities between them and the endoplasmic reticulum of mammalian cells and of the plastids of plant cells. A complete identification awaits a knowledge of the function of this cytoplasmic system in the bacterial cell.

Elongation of a Leprosy Bacillus (*Mycobacterium lepraemurium*) *in a Cell-free Medium*. P. D'ARCY HART and R. C. VALENTINE. Nature, **185**, No. 4705, Jan. 1960, pp. 58–60.

Though *M. leprae* was one of the first bacteria to be identified as the causative organism of a disease, full success in its culture lags far behind, and this has led to much study of the only other closely related organism, which is *M. lepraemurium*, which in rats and mice causes a disease with some of the features of human leprosy. Like *M. leprae*, it is unusually slow-growing in the body, with 10 days generation time. In 1958 there was an important advance when Rees and colleagues, Garbutt and colleagues, Wallace and colleagues observed limited multiplication of *M. lepraemurium* in tissue culture, but so far in a cell-free medium it remains uncultivated, and in its respiratory metabolism it shows an almost complete lack of response to many substances (Gray, 1952). A completely degenerate form of *M. lepraemurium* has been distinguished by electronmicroscopy by McFadzean and Valentine (1959, 1960). This form is non-viable and is unable to produce disease. In conventional culture media it appears after incubation of a few weeks at 37°C. In one experiment where the medium was a liquid nutrient with 20% added sucrose, electron-microscopy showed at 2 months that among the degenerated bacilli there were some which looked unusually long, as if some limited growth had occurred before death of the bacilli. Therefore

the authors investigated the frequency distribution of lengths after varying times of incubation of *M. lepraemurium* in different media. The bacillary suspensions were added to 6 different media and incubated at 37°C. The lengths of 100 or more bacilli from each subsequent sample were measured at × 10,000 under the electron microscope, and the proportions also estimated of completely degenerated bacilli. In 3 non-nutrient media there was no elongation of bacilli, and degeneration was rapid. In the ordinary nutrient culture media a small amount of lengthening occurred. But in the same medium with 10% sucrose or 8% glucose the mean length nearly doubled and for bacilli longer than 2.5μ the proportion rose from 6 to 67% with the added sucrose and 51% with the added glucose, the greater part of the increase being in the first 2 weeks. There was also greatly slowed degeneration. INH was incorporated in one of the media and had the effect of preventing the lengthening of bacilli, which means that the lengthening is not due to a passive stretching. The long bacilli showed no change in electron density: there was a slight increase in width. This points to a real increase in bacterial protoplasm in the cultures. Thus *M. lepraemurium* in culture medium has not a complete inability to metabolize and grow. Multiplication fails because it fails to divide. If means could be found to encourage division their culture in cell-free media might at last become possible.

The basal nutrient medium used contained:

2.5 g. of Difco "Casamino" Acids
0.3 g. of asparagine
2.5 g. of Anhydrous disodium hydrogen phosphate
1.0 g. of potassium dihydrogen phosphate
1.5 g. of sodium citrate
0.6 g. of crystalline magnesium sulphate
25.0 ml. of glycerol
1000.0 ml. of aqua dest.
added to 0.25% of bovine plasma albumin fraction (V)
added 1 to 20% of sucrose
or added 0.5 to 8% of glucose

The Initiation of a Trial of BCG Vaccine for Leprosy: J. A. MCFADZEAN and R. BHAGWAN SINGH., Trans. Roy. Soc. Trop. Med. & Hygiene, **54**, 1; Jan. 1960, p. 8.

These authors in a Laboratory Meeting described this trial going on in a static population of 7,500 Chinese on an island off the coast of Malaya .The population from birth to 25 years of age has been examined for clinical signs of leprosy and tuberculin-tested. Those reacting with 9 mm. or less to the tuberculin, which was 5 T.U. of R.T.22, have been grouped at random. One group was given freeze-dried BCG and the other left as a control. The population is to be

followed for 10 years and examined at intervals for leprosy. It was found that the intake of new born children would be too low, and this part of the trial has been abandoned, but the present population should be enough to demonstrate a level of protection by the BCG of 50%.

Histiocytic Granulomatous Mycobacterial Lesions Produced in the Golden Hamster (Cricetus Auratus) Inoculated with Human Leprosy. Negative Results in Experiments using Other Animals. CHAPMAN H. BINFORD, "Laboratory Investigation", Washington, **8**, 5: Sept.—Oct., 1959, pp. 901—923.

Dr. Binford reports on his comprehensive project in animal inoculation with human leprosy, begun in 1956 with the ultimate aim of producing lesions due to *M. leprae* which could be reproduced with regularity in an animal. The first step was to produce local progressive lesions at the site of inoculation. On about 1,500 small animals 35 inoculation experiments were undertaken, and also on 31 monkeys, and several methods for reducing host resistance were used, especially irradiation of the whole body and administration of cortisone. The factor of temperature of body sites was taken into consideration, for it is known that a temperature relatively lower than that of the internal organs is a common factor in all body sites preferred by *M. leprae*. Therefore the cooler parts of animals were selected for inoculation, such as the external ear, tail, foot, testis, scrotum, and skin, and the hair kept clipped on hairy sites of inoculation. Feldman with *M. ulcerans* found this influence of low temperature of skin was important. Binford studied the average temperatures of body surfaces in golden hamsters and found, for example, that at room temperature of 61°F. (15.1°C.) the ear temperature was 72.4°F. (20.5°C.). In monkeys the ulnar and femoral nerves were inoculated, because *M. leprae* has a predilection for peripheral nerves. In other animals the inoculations were made by multiple punctures, scarification, and intracutaneous routes, in the hope that bacilli might gain access to the terminal parts of tiny skin nerves. Human material for inoculating the animals was derived from 3 sources, Philippines, Carville, and Washington. The specimens were homogenized and the concentrations of the bacilli in the Oil-Immersion field varied from 10 to 100 bacilli. Heat-treated inoculum was used in controls. Histological studies of the inoculation sites were made regularly. Histiocytic granulomatous lesions appeared about 18 months after the inoculation in the testes and ears of the golden hamster. These lesions resembled human lepromatous leprosy in their histological picture, in the number of intracellular acid-fast bacilli, and in the presence of bacilli within nerves. Even with skin specimens that had been frozen with solid carbon dioxide and stored for 10 months, a heavy growth was produced in the ears

of hamsters when inoculated. Total body irradiation produced no evidence of influence on the infection. The animals treated with cortisone died too early to permit of an assessment of its influence. Transfer of the infection to other hamsters seems indicated by 5 months of preliminary work on this aspect. Further studies of the mycobacteria and further direct inoculation trials will be needed before final conclusions can be arrived at.

A Preliminary Report on the Effect of Diamino-Diphenyl Sulphone on Malaria in Northern Nigeria. H. M. ARCHIBALD and C. M. ROSS, Journ. of Trop. Med. & Hyg. **63**, 2: Feb., 1960, pp. 25—27.

For the past 7 years DDS has been extensively used for the treatment of leprosy in Northern Nigeria, reaching 195,000 cases at the present time. There has been widespread and rapid subjective clinical improvement and solid and steady amelioration of the disease itself. The authors wondered if there were an effect on malaria which might explain the early clinical improvement. They conducted a preliminary investigation to determine the comparative prevalence of malaria in leprosy patients under treatment and in the healthy subjects at 4 centres in Zaria Province. It was found that *P. malariae* parasitaemia had disappeared from those taking DDS and that *P. falciparum* trophozoites occur about one tenth as often compared to the corresponding untreated. There are also lesser parasite densities in those of the DDS group who show infections, and less pronounced splenic enlargement. The suppression in the DDS group is incomplete. Activity of DDS was compared with chloroquine phosphate, and it was found to be positive and considerable, but slower than chloroquine (200 mgm. of DDS was compared with 300 mgm. of chloroquine base). DDS achieves trophozoite clearance. There are very few toxic effects from 800 mgm. weekly of DDS as used in leprosy and it is cheap, and could be used as an active prophylactic or a valuable synergist with other antimalarial drugs. If, as is probable, DDS acts on the metabolic processes of the parasites at a point different from proguanil or pyrimethamine it may be able to combat the survival of strains resistant to a single drug.

REPORTS

Report from Brazil, kindly sent by DR. H. C. DE SOUZA-ARAUJO.

The attempts to cultivate *Mycobacterium leprae* in Sao Paulo (Brazil) failed.

Dr. Orestes Diniz, Director, Serviço Nacional de Lepra, was officially invited to attend the demonstration in Sao Paulo of the culture of *M. leprae*. The meeting, which was put out on television and presided over by the Secretary of Health of the State, Dr. Fauze Carlos, took place at the Instituto Adolfo Lutz, on 10th November 1959.

Drs. Murilo P. de Azevedo, Paulo Rath de Sousa and Maria Pereira de Castro stated that they have cultivated *M. leprae* in tissue culture, using biopsy of a skin lesion of a woman suffering from mycosis fungoides associated with lepromatous leprosy. The communication was illustrated with colour slides of smears of the culture, showing cells parasitized by globi. A tube of the culture was shown.

In conclusion, the authors claimed to have cultivated *M. leprae* in human tissue *in vitro*, for the first time in the world.

A summary of the communication was published on 11th November, by the periodical O GLOBO of Rio de Janeiro, which because of the importance of the matter has been cabled all over the world.

On 12th December, 1959, the three above named technicians of the Department of Control of Leprosy of Sao Paulo came to Rio and spoke at the meeting of the Associação Brasileira de Leprologia, under the chairmanship of Dr. Orestes Diniz. Their speech may be summarised as follows:—

1. The tissue culture was made with a biopsy of skin lesion from a woman suffering from mycosis fungoides associated with lepromatous leprosy.

2. Until the 40th day, smears of the culture, stained by Ziehl-Neelsen method, showed many cells with globi of typical aspect.

3. From the 80th to 120th day, the acid-fast bacilli decreased in number progressively until disappearing in the culture, without leaving detritus and granulations, in contrast with the intense multiplication of the cells.

4. New fresh cells were not added to the culture, which was transplanted on to artificial media of the type used for mycobacteria, with negative result.

5. The authors said that they were not sure that the bacillus seen was really the *M. leprae*, which did not multiply in the culture.

In conclusion, the authors denied their statement made in Sao Paulo on 10th November, and said that they have the intention to repeat the experiment using tissue culture from another case of mycosis fungoides not associated with leprosy.

Rio de Janeiro, 21st December, 1959.

Teaching in Leprology

The Faculdade de Ciencias Medicas (University of Rio de Janeiro) since April 1936 has given regular courses on leprology. Two courses were given in 1959, each of 40 theoretic and practical lectures, from March to June and from August to November, lectures being given by Professor H. C. de Souza-Araujo and his Assistants, Drs. Avelino Miguez Alonso and João Baptista Risi. The Faculty gave diplomas in leprology to 91 alumni of the 6th year of the medical course.

Spectacular Efficacy of Ciba 1906

E.B., a white man of 37 years, had his leprosy classified as tuberculoid in 1942 (Dr. H. Portugal), which progressed to lepromatous in 1945 (Dr. H. Portugal). From 1947 till 1959 he took, intravenously, about 15 litres of sulfones (6 kgs. DDS), mostly Promin. His treatment was interrupted on various occasions due to mild lepra reactions, but from May 5 1959 he has had a severe LR., in which his skin is covered by lepromata and plaques. Nasal mucus shows innumerable intracellular globi. From 5/5 till 11/8 he was subjected to 4 skin biopsies and the nasal secretion was collected for inoculation in murines.

From July 1st to Dec. 17th he took 720 tablets of Ciba 1906 (360 g.). In October his lepromas started softening. From November 7th to December 17th many smears of skin lesions and nasal mucosa were examined. After 44 years experience in the treatment of leprosy I never had reason to be too optimistic of his cure, but now I was surprised with the rapid amelioration of this patient, whose smears are showing mostly pale acid-fast bacilli, detritus, absence of granules, and mostly broken down globi in the mucus. If this case continues in such manner and be confirmed in other lepromatous cases for whom I prescribed the new medicine I will proclaim that Ciba 1906 is suitable for mass treatment. Unfortunately it is too expensive here (ten times more than Ulfasone). (The price has been reduced, and in England at present it is £3 per 1,000 tablets to hospitals. Editor.)

Leprosy Report, Western Australia; DR. W. S. DAVIDSON, Deputy Commissioner of Health, has kindly sent a report on the leprosy work there which is of great interest. It will appear in the 1958 Annual Report of the Commissioner of Public Health, and in the meantime permission has kindly been given for this summary of the Leprosy Report to appear in *Leprosy Review*.

Leprosy was introduced to Western Australia about the turn of the century, and is therefore a comparatively new disease among the aboriginal non-immune population. The picture of leprosy is there-

fore probably a truer one than in long-endemic countries. There appear to be at least three lepromatous cases for every one tuberculoid case. Neural involvement is an almost invariable feature of the lepromatous and proceeds step by step with the evolution of the disease to a degree of tissue destruction rarely seen in the tuberculoid cases there. Another feature of West Australian leprosy is its *lability*. Cases that have been regarded as tuberculoid have broken down after a number of years, and have become frankly lepromatous, with demonstrable acid-fast bacilli and a negative lepromin reaction. Under treatment the converse is also true, in that lepromatous cases have become lepromin positive parallel with a rapid clinical improvement. It has become natural therefore in Western Australia to regard leprosy classifications as applying only to the resistance being displayed to the infection at the time of examination. There is also in age incidence no suggestion that the disease is acquired in infancy, but there is a broad spread of susceptibility through age groups. Contacts who were of white race have developed the disease after apparently very brief or cursory contact. The number of white persons who have acquired leprosy in Australia is remarkably high, bearing in mind the few who are at risk and the few opportunities for infection, and the lepromatous cases are 2 to 1 against tuberculoid. It seems as if susceptibility must be linked to some intrinsic factor. "With such a hypothesis, infection may be acquired by brief contact, but prolonged contact will greatly increase the chance of the two factors being available at the same time."

In treatment their experience in Western Australia began with Diasone and Promine in 1947, and later Sulphetrone by injection, Thiacetazone, and DDS by mouth, INH, Ciba 1906, and Etisul were tried. These drugs have had a dramatic effect on the discharge rate from Derby Leprosarium. In the early days of the drug therapy patients were discharged too soon: now it is only after 2 years of negative smears. Combinations of drugs are now used. For neural cases surgery has been used, but the influence of chemotherapy has been disappointing until recently, when Ciba 1906 has brought more promising results, and the use of intra-neural hydrocortisone is being tried as an adjuvant. Ciba 1906 also has a very satisfactory effect on the general wellbeing and mental attitude of the patient. DDS, on the other hand, has seemed to have a low-grade toxicity which is anti-euphoric. They think a good plan of treatment would be to start with Ciba 1906 for the first year possibly with Etisul added during the early months. Later DDS may be used with Promacetin or INH plus Thiacetazone as alternatives for DDS when the latter is badly tolerated.

The social and epidemiological effects of the new therapy are good. Patients come voluntarily for treatment and cases are seen much earlier. The need for isolation is not considered to be abolished,

but greater surveillance in the field is being developed. A medical officer has been appointed to help control the endemic diseases of the aboriginals and he will examine all persons in order to detect leprosy at an early stage, and to supervise contacts, and the aim is complete eradication of leprosy, perhaps in the next decade. For whites, segregation may be in home conditions after a period of stabilisation in hospitals. The low toxicity of Ciba 1906 makes this plan quite practical. Prophylactic BCG has been confined to infants born in the leprosarium. They are removed at birth to the care of Mission bodies or foster parents.

In the leprosarium, which dates from 1935, in 1952 for the first time in its history there were more discharges than admissions, and that has remained so ever since. In 1951 there were 333 patients at the end of the year, and in 1958 there were 150, and discharges had risen to 65.

Western Nigeria Campaign to Eradicate Leprosy: Government's New Battle to Remove Public Fears of the Disease. "News from Western Nigeria", 10, Bruton Street, London, W.1, has sent the following information:—

At Ossiomo, a Centre of the Leprosy Service of Western Nigeria, following on the practical experience of the curability of leprosy, they have begun to try to change the social prejudice against the disease. Ossiomo leprosy hospital was opened by the Benin Native Administration in 1930 under the direction of a woman doctor, Dr. L. M. Lengauer. It is a model village, containing not only a hospital of 160 beds, but full civic features and welfare and recreative facilities. When positive cure of the disease approaches the patients are apt to be apprehensive about their welcome when they leave and enter civic life. There is the fear of ostracism and public indignity and the application to them by the public of the stigma of having been in the leprosy "colony". The Health Minister, Mr. J. O. Adigun, analyses the task of eradicating the fear and stigma of leprosy as an educational job in the main. The subsidiary leprosy treatment centres which have been set up in every town and village in the area help considerably in the diffusion of the knowledge and understanding of leprosy which combats irrational prejudice. They have already made some impact on the tendency for leprosy patients to consult "bush doctors" whose only remedy is to apply a corrosive fluid to the lesions of leprosy. They also hope to persuade more and more patients to come forward, by a policy of rehabilitation as well as cure of the disease. Western Nigeria aims at nothing less than eradication of leprosy.