

LEPROSY REVIEW

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EDITORIAL

I. Symposium on Leprosy Research, London, 20th June, 1960

Through the courtesy and cooperation of the International Academy of Pathology, Dr. R. J. W. Rées of the Acid-Fast Club of London was able to organise a Symposium on Leprosy Research in the Royal College of Surgeons, London. This occupied the whole of the day, was very well attended and yielded a fine crop of interesting papers and discussions. Dr. C. H. Binford kindly acted as Chairman of the morning session and Dr. P. D'Arcy Hart of the afternoon session. Excellent demonstrations were on view, namely, "Suggested Pattern of the Evolution of Leprosy", by R. G. Cochrane, London; "The Inoculation of *M. leprae* into the Golden Hamster", by C. H. Binford, Washington; "Histology of Peripheral Nerves in Leprosy", by D. G. Jamison and Elisabeth Palmer, Oxford; "Growth of *M. lepraemurium* in Macrophage Cultures", by Y. T. Chang, Bethesda. In the evening members of the Acid-Fast Club and visitors had an enjoyable dinner together in a London hotel. The whole day was a red-letter one, and all leprosy workers will be grateful for the alertness of the Acid-Fast Club to seize this opportunity, and for what they made of it.

1. Dr. R. Chaussinand of the Institut Pasteur of Paris gave the first paper on "*Quelques Indications Théoriques et Pratiques Resultant de nos 28 Années de Recherches sur la Lèpre* (Some Theoretical and Practical Ideas Arising from our 28 Years of Research into Leprosy). In some preliminary remarks he drew attention to the difficulty of first class research being done in remote leprosy research centres and of the value of liaison with central leprosy research centres, and of the necessity for WHO to take a practical interest in fostering leprosy research. In his paper, which was read in English by Dr. Rees, he described his studies in the morphology and grouping of *M. leprae*, showing that there existed normal, involuted, divided, and degenerate bacilli, and that there was a difference between a mass of bacilli and a globus. The globus in practice belongs only to lepromatous, prelepromatous and borderline leprosy. Morphological data are often neglected by leprologists but still remain important in the evaluation of the infection. He drew attention, in staining the bacillus, to the value of Sudan Black, which he has used for a long time and reported on as valuable in distinguishing mycobacteria from each other. Because *M. leprae* does not stain with Sudan Black, for some years the author has been searching in vain for a cultivable acid-alcohol-fast mycobacterium which does not stain with Sudan Black. Since 1932 Chaussinand has made repeated attempts at culture, without success. The basic problem is that of finding suitable culture media. In animal inoculations he obtained best results with the guinea pig and the monkey by grafting of leproma. A localised

leprotic infection was induced, but it died out. There was some success in transferring the infection from an infected guinea pig to a healthy one, but this infection also died out. Intraperitoneal inoculations of *M. leprae* to the rainbow perch (*Eupomotis gibbosus*) resulted in dissemination in the body and persistence in the liver and spleen for more than three-and-a-half years. There were some cases of death of the fish from bacillary embolism, which never occurred when the Stefansky bacillus was inoculated. The latter bacillus could keep its virulence for more than three-and-a-half years and infect the white rat when inoculated from the rainbow perch. Perhaps experiments with other cold blooded animals should now be tried. In his work on lepromin he found Wade's method the best. He made a standardised lepromin using the same technique each time and nodular material from different sources. Dilution to 1/50 turned out to be practical. In immunity he points out the influence of *M. tuberculosis* and vaccination and revaccination with BCG. The hypothetical natural "N factor" of Rothberg does not seem real, as it smacks of "predestination" applied to the evolution of the leprosy infection.

2. Dr. H. W. Wade, of Culion, Philippines, expounded his concept of the *Histoid Leproma*. Dr. Wade gives the name "histoid" to a variety of leproma, of which *one peculiarity* is its histological resemblance to an organised tissue which might be called fibromatoid, originating in connective tissue. The lepra cells tend to elongate more or less and to line up in rows separated by reticular or collagen fibres or both. This element is delicate and inconspicuous in young active lesions or parts of them, tending to distinct fibrosis as it stains deeper. The *other peculiarity* of histoid leproma is an absence of globus formation, because the lepra cells fail to produce the gloeal matrix. In the active lesions the cells contain large numbers of bacilli but do not vacuolize. There are some exceptions, rarely, where limited areas of a lesion show globi or vacuolated cells of xanthoma type, and there has been the rare finding of distinct tuberculoid foci inside the mass of a histoid lesion. The *third peculiarity* of histoid lesions is the tendency to enlarge by expansion from within rather than by infiltrating peripherally, a thing which typically ends up in producing well-defined intradermal or infradermal nodular masses. These may ulcerate and cause deformities. Areas within a given nodule vary greatly, and there is a tendency to small scale "reactions" in the nodules, leading to focal softening and sometimes small abscesses. Cases with histoid lesions cannot be identified clinically with certainty, but patients with especially prominent and sharply defined cutaneous nodules, and with persistent subcutaneous nodules, are likely cases for histoid lesions. Such cases seem liable to fail to respond to treatment. Non-nodular histoid lesions probably occur fairly commonly, but histopathologists do not recognise them as distinctive, and it is not known

whether such cases differ in later evolution and prognosis from patients with classical lepromas. There has been one complex borderline case, in which the diphasic lesions showed a lepromatous element which was non-nodular histoid. The histoid condition is worthy of study, correlating the clinical aspects with the histological.

3. Dr. V. Møller Christensen of Roskilde, Denmark, with many informative slides described *Osseous Changes in Mediaeval Leprosy* as studied in 92 complete skeletons from the mediaeval graveyard of St. George's Court in Naestved in Denmark, dating from 1250 to 1550 A.D. Traces of pathological changes typical of leprosy were found in these, viz: 94.5% had inflammatory changes in the nasal cavity and 82% had deformities of the hands and feet. There were also 111 skulls found separately in the graveyards which showed the same pathological changes. That makes 198 skulls which showed the signs of inflammation in the nasal cavity, the predominating being atrophy of the anterior nasal spine in 75.5%, central atrophy of the alveolar process of the maxilla in 67.1%, and increased bone in the orbit in 63.6%. The heavy incidence of chronic inflammation of the nasal cavity may have been a feature of mediaeval leprosy, and perhaps there may have been a causal connection but in modern leprosy, atrophy of the anterior nasal spine and atrophy of the maxillary alveolar process still remain common.

4. Drs. D. G. Jamison and Elisabeth Palmer of Oxford described *The Histological Changes in Leprosy and Their Modification by Treatment*. With illustrative slides they first described the histology of the three main types of leprosy as found in Northern Nigeria. The anaesthetic *tuberculoid lesion* showed absence of nerve fibres and of bacilli, and the presence of the typical granulomatous infiltrate with giant cells, epithelioid cells, and lymphocytes. In a silver-impregnated section of skin there were completely denervated hair follicles and no staining of other nerve fibres, considerable destruction of nerve fibres in the bundle running to a lesion, an infiltrate within the epineural sheath similar to that in the skin. In the *lepomatous lesion* the infiltrate has a large number of bacilli and the silver section shows the cutaneous nerve bundle with little reduction in the number of axons but an increased argyrophilia, and regeneration as well as degeneration of axons. In *dimorphous lesions* there is a mixed picture. For study of the effects of treatment material was taken from patients by using a 2 mm. biopsy punch, after infiltrating the skin with 2 ml. of procaine to which 1 ampoule of Hyaluronidase had been added. Each specimen was stained with haematoxylin-eosin to show the general histological picture, with a combination of haematoxylin and the Fite-Faraco method to show up the bacilli, and with Schofield's modification of Bielschowsky method to show innervation. Also, serial silver-impregnated sections were counterstained by the Fite-Faraco method to show the relationship between bacilli and nerve

fibres. The treatments given in the cases studied were DDS in Katsina outpatient centres, and in the Katsina Leprosarium, Etisul inunctions. The biopsies showed progressive reduction of infiltrate, often in advance of clinical signs of improvement, as well as a progressive decline in the number of bacilli in the skin. Bacilli were still to be found in the Schwann cells of peripheral nerves after 18 months of DDS therapy, although by that time they had disappeared from the skin.

As Etisul is a new drug under trial, more details are given.

(a) *Four cases under Etisul for 9 months* (inunction of 2 tubes a week). Of these the first case was dimorphous, a boy of 8 years, who was in a state of reaction to DDS, and this treatment was stopped when Etisul was begun. A biopsy taken before Etisul shows sections with dimorphous infiltrate. Biopsy from the same case after 9 months of Etisul shows a marked reduction in perivascular infiltrate, and a greater number of fibrocytes is seen in the infiltrate.

The second case was a child with 2 tuberculoid patches, who when first seen had signs of DDS reaction. After 9 months of twice weekly inunction of Etisul the histology shows less density in the tuberculoid infiltrate, epithelioid cells are fewer, and there is increased fibrosis at the edges.

The third case was a girl of 5 years with multiple dimorphous macules, and a state of reaction after 6 weeks of DDS administration. After 9 months of Etisul twice weekly the histology shows some improvement and acid-fast bacilli seem to have disappeared, though there were some in the first biopsy.

The fourth case was very advanced lepromatous, untreated. Here biopsy sections after 9 months of Etisul show almost complete disappearance of bacilli (the skin of the back).

(b) *Daily application of Etisul was tried in lepromatous patients for 3 weeks.* They had received very little previous treatment with DDS. Dr. Dreisbach kindly assisted in the selection of suitable patients, and provided laboratory space.

The first case showed, after 3 weeks of Etisul daily, a dramatic reduction in the density of the infiltrate and a complete disappearance of bacilli from the infiltrate. However in a section silver-impregnated and counterstained for bacilli, unaltered bacilli were seen in close relationship to the cutaneous nerve fibres, actually lying within the Schwann cell cytoplasm. In that same section some granular bacilli faintly stained were to be seen in the surrounding connective tissue.

The second lepromatous case also after 3 weeks of daily Etisul shows a great eradication of bacilli, and again the cutaneous nerve bundle shows acid-fast bacilli of normal appearance lying close to the axon.

The biopsies were taken from the scapular region before and after treatment in adjacent sites.

5. Dr. G. R. F. Hilson of London gave a paper on *Immunological Studies in M. lepraemurium Infections in Rats*. He investigated the immunological relationship between BCG and *M. lepraemurium* by injecting white rats with various combinations of living and heat-killed BCG and *M. lepraemurium* suspensions. A subsequent intra-testicular injection of living *M. lepraemurium* was given (usually 8 weeks later) to test the effect of the primary inoculation, and any multiplication of the challenge inoculum was estimated by making counts of acid-fast bacilli in testis homogenates. The results indicated that inoculation with living or killed *M. lepraemurium* produces an immunity which is barely detectable, and the combination of killed *M. lepraemurium* with living BCG is also ineffectual. Heat-killed BCG has the most immunizing effect, considered on a weight for weight basis.

6. Prof. J. M. Robson and Drs. J. T. Smith and F. M. Sullivan of London reported on their studies on *The Effect of Vaccination with Various Mycobacteria on the Multiplication of M. lepraemurium in Mice*. When *M. lepraemurium* is inoculated into the cornea of mice there is rapid multiplication there for about 6 weeks, but after this the rate slows down considerably. This might be due to immunity. Therefore a previous vaccination with *M. lepraemurium* was given to the mice, and after a period had been allowed for the development of possible immunity it was found that the organisms did not multiply in the corneas as much as in the control mice. BCG vaccination also had this effect but there was none from *M. leprae*.

7. Dr. D. S. Ridley of London gave a paper on *The Nature of the Lepromin Reaction: Histological Observations*. He recalled that patients who are positive to lepromin react to extracts of normal skin much the same way as to lepromin, and in an attempt to compare these reactions he obtained serial biopsies of reaction sites in co-operation with Dr. T. F. Davey of Uzuakoli, Eastern Nigeria. He found a vigorous eosinophil and polymorph cell infiltration as soon as 4 hours after the injection of lepromin. Later micro-abscesses developed in many cases and at that stage quite large fat accumulations could be noted. In over half the cases at the 4th week the Mitsuda reaction comprised a foreign body reaction to the fat; in the rest of the cases it was a reaction of tuberculoid type, with further tissue necrosis. Because of its timing and character, he thinks that the immediate reaction is one of hypersensitivity. Tissue breakdown during the reaction is what causes the appearance of fat. The explanation for the two types of Mitsuda reaction is still not clear. He found that the reactions to normal skin and to lepromin were essentially the same, and clinical and histological characters correlated only vaguely in quality, quantity and time.

8. Dr. K. R. Chatterjee of Calcutta (now in London) gave a paper on *Observations on a Mycobacterial Infection in a Hybrid Strain of Black*

Mice Inoculated with Human Leprosy. He described his inoculation experiments in the Calcutta School of Tropical Medicine (reported first in 1958) and thought that the encouraging results were due to the use of bacillary suspensions freed from tissue elements by differential centrifugalization, and to the use of a selected hybrid strain of black mice bred under controlled supervision. There were 124 mice in the experiment. Inoculations were given to 56 of *M. leprae* which had been freshly isolated from 6 different human patients. The remaining 68 mice were re-inoculated with bacilli from the first mice. Infection to the 4th passage was maintained in some, but within 5 or 6 months of inoculation progressive infection was not observed, though heavy infections were obtained in the following 6 months. Of the 56 mice who received human bacilli directly, 30% showed mild infection, 10% moderate, and 3.5% showed generalised heavy infection. The internal organs (liver, spleen, lymph glands, omentum, ovaries) and the skin and peripheral nerves and the testes showed intracellular and extracellular acidfast bacilli. In heavy infections the cells were packed with bacilli, with displacement of the nucleus and disappearance of the cytoplasm. The possibility that the infection was due to the tubercle or saphrophytic acid-fast bacilli was excluded by inoculation of culture media with infected mouse tissues, wherein no growth was obtained. The bacillus of Stefanskii was excluded because inoculation into albino rats failed to produce the disease. A Dharmendra type lepromin was prepared from infected mouse tissues and tested on cases of human leprosy and gave a normal pattern of response, which shows that the bacilli from the mouse lesions are antigenically similar to *M. leprae*, a similarity which is not shared with the bacillus of Stefanskii or with several other strains of acid-fast bacilli.

9. Prof. N. Dungal of Reykjavik, Iceland, gave a paper on *Is Leprosy Transmitted by Insects?* He thinks that the way is still open for profitable study of insects as possible agents of the transmission of leprosy. The skin seems to be the main portal of entry of the bacilli, but the entry of the immobile organism into the skin is still not satisfactorily explained. Surely biting insects can be visualized reasonably as having a role here. But which insect? Prof. Dungal sent out an enquiry round the world about the prevalence of 10 species. Replies came from 42 places. Some insects could be excluded as vectors as they did not exist in half or more of the countries. *Pediculus capitis* and *P. pubis* were reported from every country with leprosy endemicity, and *Pulex irritans* from 39 out of the 42 countries, and there are several suggestive arguments for this flea being the vector. Transmission by flying insects is probably rare, but *Acarus scabiei* is a possible. G. Muñoz Rivas of Colombia made experiments with fleas and acarus and found acid-fast bacilli in them, and a living association of these insects with leprosy patients. Prof. Dungal suggests that

some isolated island where leprosy is prevalent be selected for an attempt at eradicating leprosy by extermination of all ectoparasites of human beings, especially lice, fleas, and *Acarus scabiei*.

10. Dr. J. R. Innes of London gave a report on his investigations of *The Russian Literature on Leprosy*. The occasion for this was that in 1959 Prof. N. A. Torsuev of the Chair of Skin and Venereal Diseases of the Rostov-on-Don Medical Institute compiled and issued in printed form "Bibliograficheskii Ukazetel Rabot Otechestvenikh Avtorov po Lepre" (Bibliographical Index of Papers on Leprosy by Russian Authors) up to the year 1957, inclusive. This bibliography contains a total of 2,620 items, serially arranged, of papers and publications dealing with leprosy, given alphabetically under authors' names. Serial Nos. 1976-2620 consist of foreign authors and the names, titles, and references are printed in the Roman script so will be readily intelligible to most Western workers, but Nos. 1-1975 are of Russian authors and the names, titles, and references are given in the Russian script and language. It seemed clear that its usefulness in the West would be enormously enhanced if this Russian section were rendered into English, and this Dr. Innes did, and distributed cyclostyled copies of the same to those present at the meeting. (Other copies remain and if any desire them they should write to Dr. Innes at 8 Portman Street, London, W.1.) Copies of the original printed bibliography of Prof. N. A. Torsuev may be obtained by request to him: he will welcome exchange of literature. The great advantage of this bibliography and of the English rendering of the same is the inclusive nature of it up to 1957. Papers can be identified and asked for by serial number. (See article in this issue of *Leprosy Review*, p. 278.) Since 1957 there has been periodical issue of "Uchenie Zapiski Instituta po Izucheniyu Lepri" (Scientific Notes of the Leprosy Research Institute) which also no doubt could be obtained through Prof. Torsuev.

11. Dr. C. H. Binford of Washington gave a *Progress Report on Animal Inoculation with Human Leprosy* which he illustrated with many excellent slides. During the past 4½ years he has carried out many experiments in species of laboratory animals to inoculate human leprosy. 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, particularly irradiation of the whole body and administration of cortisone. The factor of temperature of body sites was also applied and the cooler parts of animals were selected for inoculation, such as external ear, tail, foot, testis, scrotum, and skin, and the hair kept clipped on hairy sites of inoculation. In the 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 cutaneous nerves. Human material for inoculating the animals was obtained from the Philippines, Carville, and Washington. The specimens were homogenized and the bacillary concentrations under the Oil-Immersion varied from 10 to 100 bacilli per field. Heat-treated inoculum was used in controls. The inoculation sites were studied regularly by histology. The golden hamster yielded the most interesting results, in that histiocytic granulomatous lesions in testes and ears appeared about 18 months after the inoculation. These lesions resembled human lepromatous leprosy in their histological picture, in the number of intracellular acid-fast bacilli, and 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 of bacilli was produced in the ears of hamsters when inoculated. Total body irradiation produced no evidence of influence on the infection and cortisone-treated animals died too early to permit of any assessment of its influence. After 5 months of preliminary work several hamster to hamster passages have been made and attempts to infect other laboratory animals. The mycobacterium of the granulomatous infection of hamsters will grow on artificial media.

12. Dr. K. R. Chatterjee and R. Bose of Calcutta described their *Observations on Immunological Reactions in Leprosy with Fractions of Kedrovskii's Bacillus*. From this bacillus they obtained 9 chemical fractions. Three of them, A, B and C, were found to give early lepromin reactions of the Dharmendra type or positive complement fixation tests in leprosy. About 1,015 leprosy cases of all types were given skin tests with the 'A' fraction and found to give the same pattern of positivity as with Dharmendra lepromin. Then complement fixation tests with 'B' and 'C' fractions were carried out on 279 leprosy patients of all types, 139 patients with Wasserman-positive syphilis, 104 cases of kala azar and dermal leishmaniasis, 100 cases of active pulmonary tuberculosis and 50 healthy subjects. Of the leprosy patients, 70% reacted positively with 'B' fraction also with 'C' although weaker, compared with 2.3% of all the others tested. These fractions also reacted selectively in the immunological tests: fraction 'A' failed to give uniform complement fixation reactions and fractions 'B' and 'C' failed to give skin reactions.

13. Dr. P. D'Arcy Hart of London discussed the *Problem of "Growth" of M. lepraemurium in vitro*. At first sight the prospects are hardly rosy for success in obtaining multiplication of this organism in cell-free media, in view of the difficulties in tissue culture, though as these difficulties are overcome much may be learned to assist in cultivation in cell-free media. Until then experience with other micro-organisms which resist cultivation may reasonably be used in the approach to cell-free media. There have

been numerous earlier fruitless attempts at nutrient media for *M. lepraemurium* and these are of value by way of exclusion, and more recently workers have been guided by (a) the lack of response of the respiration of *M. lepraemurium* to the usual substrates which are potentially stimulating; (b) protection against a possible toxic effect of serum by substances such as albumin and yeast; (c) possible defect of entry of nutrients, metals, etc., into the organisms; (d) possible peculiarities of their surface; (e) possible requirements of special nutrients, as in the analogy of mycobactin for Johne's bacillus. There has been no success as yet along these lines but D'Arcy Hart and R. C. Valentine have recently reported the elongation of *M. lepraemurium* in a cell-free medium (*Nature*, **185**, No. 4705, Jan. 1960, pp. 58–60). Like *M. leprae* it is unusually slow growing in the body, with a generation time of 10 days. In 1958 there was an important advance when Rees, *et al.*, Garbutt *et al.*, Wallace *et al.* observed limited multiplication of it in tissue culture, but so far it remains uncultivated in a cell-free medium, and its respiratory metabolism shows an almost complete lack of response to many substances (Gray, 1952). Then McFadzean and Valentine (1959, 1960) distinguished by electronmicroscopy a completely degenerate form of *M. lepraemurium* which is not 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, by electronmicroscopy at 2 months there were seen among the degenerated bacilli some which looked unusually long, as if some limited growth had occurred before the death of the bacilli. Therefore D'Arcy Hart and Valentine investigated the frequency distribution of lengths after varying times of incubation in different media. The lengths of 100 or more bacilli from each subsequent sample were measured at X 10,000 under the electronmicroscope, and the proportions also estimated of completely degenerated bacilli. In 3 non-nutrient media there was no elongation, and degeneration was rapid. There was a small amount of elongation of bacilli in the ordinary nutrient media. But when 10% sucrose or 8% glucose was added the mean length nearly doubled. The proportion of bacilli longer than 2.5μ rose from 6 to 67% with the added sucrose and 51% with glucose added, and the greater part of the increase took place in the first 2 weeks. There was also slowed degeneration. INH was incorporated in one of the media and had the effect of preventing the elongation of bacilli, which suggests that it is not due to a passive stretching. More recently magnesium ions have been shown by these authors to stimulate lengthening with or without the sucrose. The long bacilli showed no change in electron density; there was a slight increase in width, which points to a real increase in bacterial protoplasm in the cultures and to there being some ability to metabolize and grow. Multiplication fails because the

bacilli fail to divide, and if means could be found to encourage division their culture in cell-free media might at last become possible. This work continues.

14. Dr. R. J. W. Rees of London gave a paper on *The Use of Cell-Cultures for the Cultivation of M. lepraemurium* in vitro. Since 1958 definite but limited multiplication of *M. lepraemurium* in vitro has been reported using a variety of cell-cultures^{1,4}. Multiplication was usually limited to one or two generations but the bacilli appeared to divide at the same rate (every 10–12 days) as *in vivo*. Multiplication occurred at 34–37°C. and was inhibited by streptomycin and/or isoniazid^{1,2,4}. Successful multiplication was obtained both by infecting the cells *in vivo*^{2,3} or *in vitro*^{1,3,4}. One possible factor limiting multiplication was the deterioration which inevitably occurred in the host-cells between the third and fourth weeks. New techniques were therefore developed for subculturing the infected cells, approximately every three weeks, in order to maintain a healthy population of host-cells. This method has resulted in more continuous multiplication of the bacilli in some of the cultures. In one experiment the bacilli continued to multiply in the cells for 150 days (after which the cultures were contaminated). Furthermore, bacilli recovered from the cultures at day 150 and injected into mice produced a typical and progressive infection. Unfortunately the method does not regularly result in continued multiplication of *M. lepraemurium*. It is suggested that even under these more favourable conditions for tissue-culture the metabolic activity of the host-cells is inadequate to support regular multiplication of the intracellular bacilli.

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II. Reconstructive Plastic Surgery in Leprosy; Lectures by Mr. Paul Brand, M.B., F.R.C.S., in Berne, Switzerland.

Surgeons and orthopaedic surgeons of Switzerland, and also the general public interested in leprosy relief, had the privilege of hearing Mr. Paul Brand explain the principles governing this art, and the preventive principles for such leprosy deformities. The first lecture was held in the Surgical Clinic and second lecture was given at a function in the Schweitzerhof Hotel in Berne, and both were illustrated with very instructive films. His Excellency the Indian Ambassador to Switzerland, Shri M. K. Vellodi, had the idea of arranging for Mr. Brand to give these lectures when he heard that Mr. Brand was touring Switzerland at the time. Messrs. Ciba of Basel helped with the expenses and Shri M. K. Vellodi and Shrimati Vellodi were responsible for the delightful evening reception. The Editor attended these functions. Mr. Brand is a very clear thinker and

a great teacher and his exposition of the causes of leprosy deformities and how the patient can be protected from developing such, and if they have irrevocably developed what are the operations which can relieve them, left all his hearers with a very definite knowledge and even an enthusiasm for these things. There is no doubt that Mr. Brand's thinking and work has started the revolution by which the common practice of doing precious little for leprosy deformities is beginning to change into the recognition that every piece of leprosy work should include provision for the prevention and surgical cure of deformities and cosmetic damage in the patient. India has become a centre of light and leading in these matters because there is the group of Brand and his colleagues at Vellore and the other group headed by Dr. N. H. Antia at Bombay. We hear that Mr. Brand is at present seeking finance for an enlargement of his centre at Vellore and that Dr. N. H. Antia is seeking to establish a special centre in the J. J. Hospital in Bombay. Both these projects can be fully recommended.

Considering that there must be millions of patients in the world today who are in need of the benefits of this sort of work, the Editor during a discussion of the first of Mr. Brand's lectures was emboldened to suggest that orthopaedic and plastic surgeons in Switzerland (and indeed in all Europe) might be interested in asking for Sabbatical leave to go to India to study these techniques, and thereafter become available on a valuable list which the Editor (in his capacity as Secretary General of the International Leprosy Association) would use to suggest to governments of African and other territories a surgeon who would be willing to go for a short time later, perhaps every year, and preferably to an African university or teaching centre, to undertake this sort of surgery. The same thing might well apply to physiotherapists, for physiotherapy is a very important part of the prevention and cure of these disabilities. This idea was received in a very friendly spirit and we hope that something will come of it.

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EPIDEMIOLOGICAL AND IMMUNOLOGICAL SURVEYS IN NETHERLANDS NEW GUINEA

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Epidemiology

SLOAN AND LEIKER¹ carried out the first systematic surveys in 1952 in Netherlands New Guinea, and even at that early stage noted marked differences in prevalence and type rate in the different parts of the country, and also strong evidence of the recent introduction of leprosy in several areas. After 1952 Leiker extended and intensified these systematic surveys, and was helped by the collection of valuable data by some district government medical officers. At the end of five years he could draw a fairly accurate picture of the leprosy situation.

In some areas it has been possible to trace the course of the endemia from its first introduction, and representative areas were studied in detail and revealed a strikingly different pattern. In the method of survey an accurate record was first made of the inhabitants of every house in the village, and then medical examination made of the total population. This procedure was repeated annually, care being taken to examine inhabitants in temporary residence elsewhere. An almost complete survey was thereby attained in a few years. Much effort was put into education about leprosy during and between the surveys, and this generated increasing interest in the disease, very good cooperation from the people, and much voluntary giving of information. The oldest inhabitants in areas where the disease was well known gave valuable information. They were asked about lepromatous patients who had died before the survey was made. No enquiry was made about tuberculoid patients, because there is a good chance of confusing this leprosy with crippling forms of yaws, and similar diseases. Because in many areas leprosy is a recent disease there were still old people living who had known intimately the first lepromatous patient in the village. Verification of the information was obtained from informants in other villages. Genealogical tables were prepared for all deceased and living patients, and extensive data obtained about the origins of families, clans, and villages, and other inter-relationships. Verification of data could be obtained by referring to events which were of local importance, e.g., the arrival of the first missionary, the opening of the first school, the presence of a well known teacher or government official. There is strong evidence that leprosy was introduced

1850
between 1800 and 1805, into some villages of the Radja Ampat Island group, in the west of New Guinea. Between 1850 and 1900 the Biak and Numfor people were infected; they had previously migrated to these islands. Leprosy did not spread from these islands until about 1870 when Numfor people brought it from these islands to Manokwari where they settled at the centre of the north coast of the mainland. The Dutch missionary, van Hasselt, in 1879 stated that the number of leprosy patients at Manokwari was increasing, which is the first written mention of leprosy. The missionaries lived in the village and knew every inhabitant and often treated their diseases and the fact that their early reports seldom mentioned leprosy supports the idea that the disease is of recent introduction in most parts of New Guinea.

The first patient in Wandamen Bay was seen about the year 1903. The son of this patient was alive at the time of the first survey and confirmed this information. Since then leprosy has spread over the interior area, and the history of this spread can be traced almost completely. In 1957 the last survey found an incidence of 80 per thousand. Further spread of leprosy along the coast of New Guinea has taken place in this century, and the spread of leprosy to the interior has been discovered in the past 30 years. This is a serious matter. A modern anti-leprosy campaign has been started in the coast area, with good hope of success within a reasonable time, but the inland situation is unfavourable and difficult.

This recent inland spread of leprosy follows from increase in the amount of contact between the more sophisticated coastal people and the backward tribes of the interior. Contact was previously limited to incidental trade, warfare, and slave hunting. Personal contact and house contact were exceptional. In the present era after pacification inland people show a growing tendency to move to the coast and set up an increasing number of villages at the coast. Even though coastal people still feel superior to the bush people there is a considerable amount of intimate contact and even intermarriage has occurred. Knowledge of the history and customs of the peoples is of utmost importance for understanding the variable patterns of disease in New Guinea. This paper will deal with some representative coastal and inland peoples who now live in the same area.

West New Guinea in the coastal part was ruled for many centuries by the Indonesian sultans of Ternate and Tidore under four radjas who were settled on some islands of the Radja Ampat Island group ("four kings"). Indonesian and part-Indonesian descendants are still living in some of these villages. These so-called "Maja" groups are considered to represent the oldest leprosy foci in New Guinea. About 400 years ago several groups of Biak and Numfor peoples migrated from their islands which lie north of Geelvinck Bay and the sultans allowed them to settle on some islands of the Radja Ampat

group. They were sea-going people and they stayed at the coast, and the local population of the islands dwelt in the interior.

Numfor people settled on the small islands of Doom, Jefinan, and Arar, and the Biak people (also called the "Beser") settled at South Waigeo and many adjacent islands. The Numfor and Biak peoples comprised the second group to be infected with leprosy. Later Biak groups settled on the east and north coast of Waigeo and in a few villages on the north coast of the mainland. These groups are also called Usba, Wardo, and Sopen, and were infected in New Guinea. The Amber group inhabited the central area of Waigeo, being the first inland tribe to move to the coast and also the first of the island residents to contract leprosy. A similar situation is found at Salawati Island and on the north coast of the mainland.

As shown by maps of the close of last century there are very few villages on the north coast of west New Guinea. These are small settlements of Maja and Beser, or temporary camps of inland people for incidental trading. The movement to the coast increased greatly between 1900 and 1930 and the maps show many names of permanent or semi-permanent small villages of inland people. The Mooi tribe of the outer west part of the mainland and partly at Salawati Island moved to the coast and became the first tribe in the area to be infected with leprosy. Most of the villages were only infected after 1925, and some only very recently. The Madik, Morait, and Karoon tribes, living in the interior more to the east, were infected late, and many of their villages are still free of leprosy.

Between 1952 and 1957 repeated surveys were carried out in these areas and Table 1 gives the situation at the end of 1957.

TABLE 1
Prevalence and Type Index in Coastal and Interior People in West New Guinea

<i>Group</i>	<i>Population</i>	<i>Number of Cases</i>	<i>Prevalence</i>	<i>Lepromatous Cases</i>	<i>Type Index</i>
Maja	500	27	5.4%	11	41
Beser Numfor	3,200	129	4%	44	34
Usba Wardo Sopen	3,000	143	4.8%	28	20
Mooi Morait Madik	5,000	403	8%	48	12

It may be concluded:

1. that leprosy has spread very fast in the recently infected areas: on several occasions a higher incidence was found compared with coastal areas with a history of the disease twice as long;
2. there was a constant finding of a low type index; tuberculoid cases predominated, often with only one or a few macules;
3. the tuberculoid patients are distributed over many houses, and as a rule lepromatous cases were few or absent;
4. though leprosy is of

recent introduction, the number of adult patients is relatively high, and there is no doubt that a high proportion of the patients sustained infection long after childhood.

Herein is a striking contrast to the pattern of leprosy in most coastal tribes. The usual ideas about leprosy seem to hold true for the coast, namely that it is a disease only mildly contagious, that adults are less susceptible, that prolonged intimate contact, in family or house usually, is needed to produce transmission of the disease, with "leprosy families", "leprosy foci", and "leprosy villages" as a regular part of the picture. There is also moderate or even slow increase of the leprosy incidence, and decades pass without attaining an even distribution of the cases, and the type incidence is much higher and children are much more susceptible than adults.

In the *Ransiki* area on the west coast of Geelvinck Bay a similar development took place. Coastal people from Windesi inhabited Rumberpon Island. About 1925, leprosy was introduced into two of the four Windesi villages, and the leprosy index in the other two villages is still very low.

The nearby mainland was inhabited in this century by the Manikion tribe, but most of the tribe still live in the interior. Rarely intermarriage occurs between the Windesi and Manikion. The first infection of Manikion coastal villages took place in the last two decades. Further over to the interior most villages are still free of leprosy. The present situation is given in Table 2.

TABLE 2

Prevalence and Type Index Rumberpon Area

<i>Group</i>	<i>Population</i>	<i>Number of Cases</i>	<i>Leprosy Index</i>	<i>Lepromatous Cases</i>	<i>Type Index</i>
Windesi (Rumberpon)	430	38	8.8%	13	33%
Manikion	950	49	5.2%	4	8%

Here also the recently infected Manikion villages show a high prevalence, a low type index, distribution of patients over many houses in the village, and a relative preponderance of adult patients. Leprosy is spreading rapidly to the interior and follows the same pattern as described above.

In *Kaimana* the disease has followed the usual coastal pattern after some coastal villages were infected about 1920. On the mainland lives the inland tribe, the Mairasi, of whom a small group settled at the coast in this century at Lobo. A second group lives inland about one day's walking distance from Lobo. The first leprosy case appeared

at Lobo between 1930 and 1940. Further spread to the interior was noted during the war. The situation is given in Table 3.

TABLE 3

Prevalence and Type Index Kaimana

<i>Group</i>	<i>Population</i>	<i>Number of Cases</i>	<i>Leprosy Index</i>	<i>Lepro- matous Cases</i>	<i>Type Index</i>
Coastal groups	1,815	83	4.6%	19	23%
Maidasi	324	36	11%	2	6%

Once more we see that the leprosy index is high among the mountain people after only a short history of the disease, with again a low type index. This situation has been found to be repeated in other parts of Netherlands New Guinea.

The coastal pattern of leprosy in New Guinea is much the same as in many other countries and gives findings which correspond, namely:

1. the disease spreads slowly after introduction;
2. foci persist in the endemic area even after a long history, and there are families and villages with a significantly higher leprosy index than others in the area;
3. the type index is variable, but seldom lower than 20 to 25%, and often higher;
4. a relatively high proportion of cases is found among children and young adults;
5. contact with lepromatous leprosy is evident in a high percentage of the new cases: this contact is very often prolonged intimate house contact, and often family contact.

Among people who have lived in relative isolation until recently the pattern is very different, namely:

1. the disease spreads fast after its introduction;
2. cases are distributed over many houses, and foci seem to be of minor importance;
3. the type index is very low, so that there is almost an epidemic of tuberculoid leprosy, and cases predominate which have only one or a few tuberculoid macules;
4. adults are almost as susceptible as children;
5. cases giving a history of contact with lepromatous patients are the minority, and even in these there has not been prolonged intimate house contact.

This epidemiology recalls the Nauru epidemic, the early leprosy history of New Caledonia, and the recent history of some parts of West and Central Africa. There are many areas with a situation intermediate between the two extremes. It is possible that the same factors operate in many countries.

A detailed study has been made of some of the areas in Nether-

lands New Guinea in order to gain more insight into the factors concerned.

Mantembu

There are two main groups in the population of Japen Island, north of Geelvinck Bay. The first group of basically coastal people, occupying villages with 500–3,000 inhabitants, has lived for many centuries at the coast. There has been some contact with the outside world for a long time. Leprosy was introduced in a few villages about 30 years ago, and in other villages even later. After these 30 years the leprosy index has not passed 3%, the type index varies between 25 and 35%, and the pattern of leprosy is of the coastal type, described above.

The second population group consists of inland people who moved to the coast 25–35 years ago. Only a few villages are left in the mountains, and a few can be found near the coast, but the majority are on the coast. These villages are usually small and the number of inhabitants does not exceed 300. The people are not yet completely adapted to life at sea, the protein intake is low, the birth rate is low, and the death rate is higher than among primary coastal people.

Leprosy was introduced in the secondary coastal villages only very recently. Several villages are still leprosy free. The village of Mantembu with 340 inhabitants was the object of a detailed study. The population moved from the mountains about 1926 and settled three miles from the coast. The first cases of leprosy appeared during the war. Thereafter the disease has spread very rapidly. After 15 years it was found that 15% of the population showed symptoms of leprosy. The first leprosy survey was held in 1952 by Sloan and Leiker. Although 80% of the population was examined and a leprosy index of 80 per thousand was found, not a single lepromatous patient was seen. The author has repeated this survey in 1954 and in 1957. The whole population was examined and the leprosy index rose to 150 per thousand. The first "infectious" patient was seen in 1954; in 1952 this patient showed a few indeterminate macules. He stated that these macules had appeared first in 1946. Smears of these macules were negative on routine examination in 1952. In 1954 the patient was classified as borderline and lesions showed 2+ smears with few globi. The people in the village denied strongly that there had ever been a lepromatous case in the village before 1954.

People show no leprosy fear, they never avoid an examination, and have always cooperated excellently. After several years of almost daily contact with these people, I am convinced that their statement is justified. They know the clinical symptoms of lepromatous leprosy quite well since a small leprosy village existed in the neighbourhood between 1934 and 1935. Also a woman from Mantembu was married in another village at the coast and her husband had lepromatous leprosy before the war. The development of the leprosy endemic is shown in Table 4.

TABLE 4
Onset of New Cases of Leprosy at Mantembu

<i>Period</i>	<i>T. cases</i>	<i>B. cases</i>	<i>Total</i>
1944-46	4	—	4
1947-49	7	—	7
1950-52	12	—	12
1953-55	15	3	18
1956	1	1	2
dubious	9	—	9

After an initial slow increase in the number of new cases, a sudden explosion of new tuberculoid cases followed and thereafter, before any effective protective measures were taken, a decrease in the number of new cases was seen.

In Table 5 it is seen that not long after introduction of leprosy, patients were found in 28 of the 39 houses in the village. Although two houses showed a particularly high prevalence, such a distribution of cases is very unusual in coastal villages, even after a much longer history. Leprosy was distributed about evenly among the sexes at Mantembu.

TABLE 5
Distribution of Leprosy at Mantembu

<i>Number of Cases per House</i>	<i>Number of Houses</i>	<i>Total Patients</i>
0	11	0
1	15	15
2	9	18
3	2	6
4	1	4
5	1	5
moved		3
Total		51

In coastal areas as a rule the prevalence of tuberculoid leprosy is much higher among females than among males; not seldom a 2:1

rate is found. The prevalence of leprosy in children is low at Mantembu. The child index is 8%. In coastal villages an index of 15–20% is usually found. A type index of 8% is very low, compared with coastal villages which usually show indices between 20 and 35%.

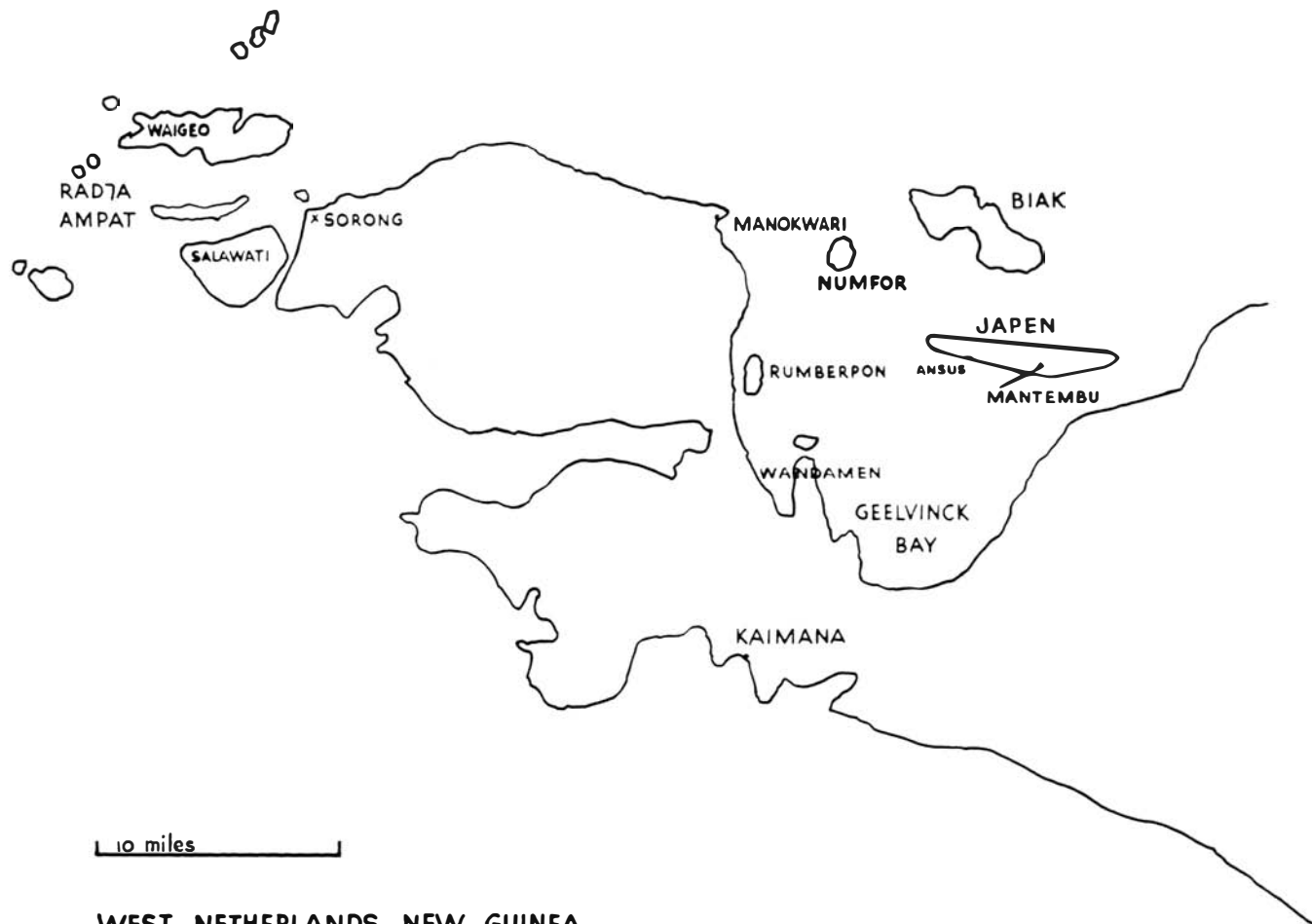
In Table 6 the attack rate per age group is shown.

TABLE 6

Age at Onset of Symptoms and Attack Rate per Age Group at Mantembu

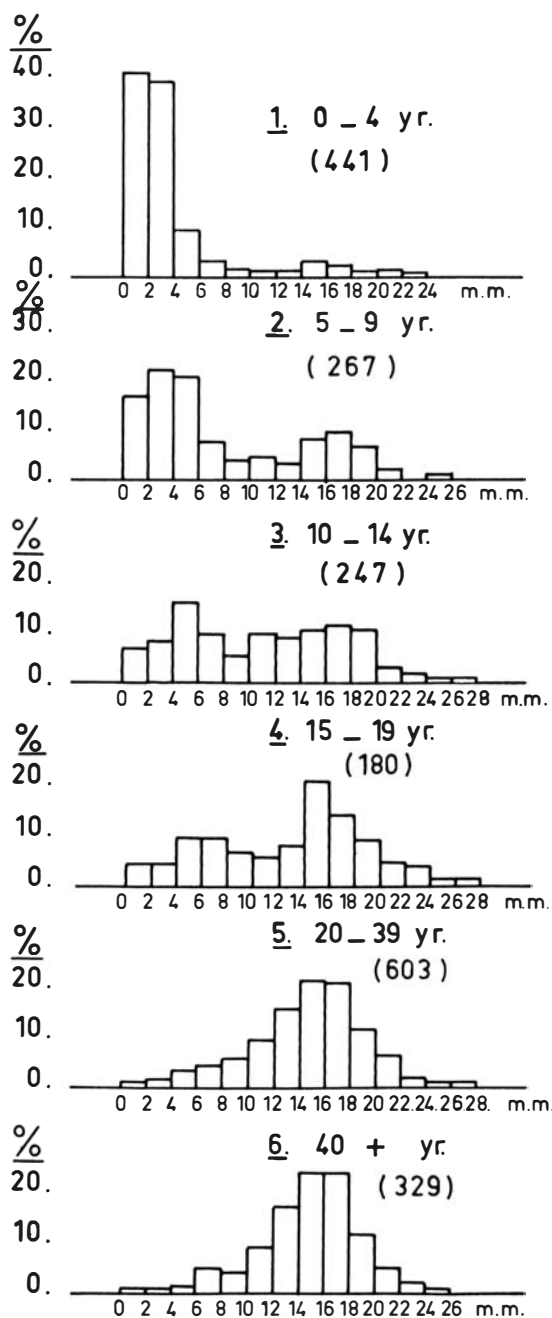
Age Group	0–4	5–9	10–14	15–19	20–39	40+ Years
Population	68	34	30	33	110	69
Distribution of Patients According to Age at Onset of First Symptoms	0 0%	5 10%	7 14%	13 26%	18 36%	7 14%
Incidence per Age Group	0%	15%	23%	39%	16%	10%

If we assume that the age distribution at Mantembu has not changed essentially during the past 20 years and if we assume that the incubation period of leprosy is in the majority of cases not much longer than 5 years, an important percentage of the patients at Mantembu must have been infected after childhood and several patients even at an advanced age. *Two sources of infection* have to be considered as a possibility. There is firstly the small leprosy village which existed in the neighbourhood between 1934 and 1935. However, the interval between the closing of the leprosarium and the manifestation of symptoms in the first patient at Mantembu is 9 years, and the majority of the cases appeared much later still. Such a long incubation period is exceptional and improbable for the majority of the cases. Besides, intimate contact with the patients was denied, which is easy to understand since the patients in the leprosarium were coastal people who came from a distant area and suffered from an unknown and serious disease. The second source of infection is more important. The fact that a woman of the clan Ambokari was married to a lepromatous man at the village Tarau implied that members of the Ambokari family also visited the house at Tarau and not infrequently spent the night there. To evaluate this source of infection genealogical tables were prepared from all patients. It was learned that 35% of the patients were in one way or another related to the Ambokari family. The two houses with the highest leprosy index were related to the Ambokari family. Although one may assume that several patients were infected by the patient at



WEST NETHERLANDS NEW GUINEA

TABLE 7
Reactions to P.P.D. 5 TU in different age groups



Tarau, there is no doubt that of the 35% of the patients who were related to this family the relationship was such a distant one that they had no intimate contact. Of the remaining 65% only a few may have had incidental superficial contact with the Tarau patient: it is certain that the majority did not have any contact at all. It is impossible to explain the epidemic at Mantembu by contact with lepromatous patients alone.

It is quite unlikely that the borderline patient discovered in 1954 has been strongly positive for such a long time. In 1952 routine smears were negative and even if repeated smears might have been positive, certainly this case was not a highly contagious one; also no further evidence could be detected that other patients were infected by this case.

The only possibility that remains is that tuberculoid leprosy has played a role in the dissemination of the disease. In our experience it is seldom necessary to assume that patients at the coast are infected by tuberculoid cases, although not always intimate and prolonged contact with lepromatous cases is evident in the majority of cases. At Mantembu, however, we have to accept the only possibility that some tuberculoid patients have acted as a source of infection. Especially the major tuberculoid and the reactional tuberculoid seem to be important. It is a well known fact that some of these cases may be rather strongly positive for some time, before becoming negative spontaneously. The survey showed that at Mantembu such cases were not rare. A history of red, raised, infiltrated lesions was obtained in several instances. After spontaneous regression, sometimes with ulceration, the asymmetrical, sharply defined, atrophic lesions were still visible at the time of the survey. It was not necessary to assume that minor tuberculoid lesions have played an important part in the dissemination of leprosy at Mantembu.

Since tuberculoid leprosy has played a part in the epidemiology in Mantembu, the population must be highly susceptible to leprosy. Factors such as climate offer no explanation. At Ansus, a coastal village with 3,000 inhabitants, on the same island, leprosy was introduced more than 25 years ago. The leprosy index is now only 10 per thousand; the type index is 35%. The disease is limited to only a few clans and within these clans a few houses show a high prevalence of leprosy.

Race, hygiene, customs, offer no explanation. At Mariadei, a village near Mantembu, belonging to the same tribe, leprosy was introduced 12 years ago. The leprosy index is 47 per thousand, the type index is 27%, the child index is 22%.

Between Mantembu and other villages of inland tribes, recently settled at the coast, and the primary coastal settlements, we have found only one important difference, the degree of isolation as a

community. We have considered the possibility that these relatively isolated groups have also remained free from tuberculosis until recently. This hypothesis is supported by the experience that although tuberculosis is a common disease along the coast we rarely found evidence of it in people living more inland. The people of Mantembu are frequent visitors at the hospital and polyclinic but we did not see a single case of tuberculosis during 4 years.

To verify this hypothesis tuberculin surveys were held at Mantembu, Mariadei, in Mooi people in West New Guinea, and also in coastal people from Wandamen Bay and West New Guinea.

Immunology

In many countries the injection of 5TU P.P.D. is followed by a very weak reaction, which does not exceed 5 mm., and which is caused by needle trauma and buffer fluid, or by a larger reaction which is caused by previous contact with *M. tuberculosis*.

In many other countries, New Guinea included, there are other unknown factors, which produce non specific tuberculin reactions. Therefore it is not justifiable to apply criteria for positivity of the tuberculin test without preliminary research.

TABLE 8
Reactions to 5 TU Human P.P.D. (2gb)

	0	4	8	12	16	20	24 mm.
+9 mm.	2	1	1				
+8 mm.	1	1					
+7 mm.			1				
+6 mm.		2	1	2	1		
+5 mm.	2	5	2	1			
+4 mm.	5	4	3	2	1		
+3 mm.	13	5	4	4	1	2	
+2 mm.	25	12	1	3	3		
+1 mm.	18	12	6	7	4	3	
0 mm.	61	10	1	4	3		1
—1 mm.	3	2	2	2	4	1	
—2 mm.			1	2	2	3	
—3 mm.			2	3	1	1	
—4 mm.	1		1	2	1		1
—5 mm.					4	2	
—6 mm.					1		1
—7 mm.						3	
—8 mm.						4	
—9 mm.					1	3	1
Average Difference	+1.2	+2.2	+2.0	+0.9	—1.0	—4.1	—5.0 mm.

TABLE 9
Reactions to 5TU Human PPD in Different Peoples in Netherlands New Guinea

	<i>MANTEMBU</i>			<i>MARIADEI</i>			<i>WANDAMEN</i>			<i>MOOI</i>			<i>SORONG</i>		
<i>Age Group</i>	<i>Number Positive % Tested</i>			<i>Number Positive % Tested</i>			<i>Number Positive % Tested</i>			<i>Number Positive % Tested</i>			<i>Number Positive % Tested</i>		
0-9 	91	5	5.5	122	8	6.6	708	104	14.7	137	4	2.9	395	57	14.4
10-19 	42	10	23.9	58	23	39.8	427	219	51.2	115	22	19.1	347	115	33.1
20 	168	68	40.5	162	121	74.9	992	724	78.1	243	113	46.5	306	205	67.0
Leprosy Index ...	15%			4.5%			8.6%			10.1%			4.4%		
Type Index 	8%			28%			28%			12%			22%		

TABLE 10
Reactions to 5TU Human PPD in a Manikion Group Living in the Interior

Age Group	0-4	5-9	10-14	15-19	20-39	40+	Total	0-4	5-9	10-14	15-19	20-39	40+	Total
Number tested	35	25	14	10	39	22	145	30	22	7	10	59	10	138
10 mm. (negative)	35	25	14	7	34	17	132	0	0	0	0	0	0	0
10-13 mm. (dubious)	0	0	0	0	2	3	5	0	0	0	0	1	0	1
14 mm. or more (positive)	0	0	0	3	3	2	8	—	—	—	—	—	—	—

Ver correção desta tabela em Lep. Rev. vol. 32 nº 3 p. 216.

We can perceive from size frequency distribution histograms of tuberculin reactions that the influence of non-specific factors increases with age. Only in young children specific and non-specific factors are more or less separated. In histograms of adults it is impossible to distinguish between specific and non-specific reactions. From histograms of young people we concluded that reactions smaller than 10 mm. were caused by non-specific factors and reactions of 14 mm. or larger by tuberculosis contact. Reactions between 10 and 14 mm. are of doubtful origin.

Further evidence was obtained by injecting human and avian tuberculin simultaneously. This was suggested by WYSMULLER² and based upon the hypothesis that in people infected with tuberculosis a homologous tuberculin would give stronger reactions than a heterologous tuberculin.

From Table 8 can be seen that in people with a reaction to human tuberculin larger than 14 mm. the reaction to avian tuberculin is on the average smaller; whereas in people with a reaction to human tuberculin smaller than 14 mm. the reaction to avian tuberculin is on the average larger. This was considered as support for the former findings that in the areas tested only reactions of 14 mm. or larger are caused by *M. tuberculosis*.

Table 9 shows the percentages of positive tuberculin reactions in different age groups from some areas mentioned in this article. There is a difference between Mantembu and Mooi people and people from coastal areas. The tuberculin index in secondary coastal villages is much lower. The difference is in all age groups statistically highly significant ($P < 0.001$).

Table 10 shows the tuberculosis situation in a leprosy-free Manikion group still living in the mountains in the interior. The tuberculosis index is very low. Women and children have a negative tuberculin reaction. This can be explained by the fact that men more often go to the coast as carriers during patrols of officials and for trading purposes. Tuberculosis is a rare disease in the interior or it has been only recently introduced.

We have seen that the tuberculosis index is low in areas where leprosy manifests itself as an epidemic of macular tuberculoid leprosy. If our hypothesis is correct that previous tuberculosis contact reduces the chance of tuberculoid leprosy then we must also expect a lower tuberculin index in tuberculoid patients compared with healthy individuals from the same area and of the same age group, at least in young leprosy foci with a low tuberculosis index. In older foci with a high tuberculosis index the chance of finding significant differences is reduced since a large number of symptom-free tuberculoid patients may have had contact with *M. tuberculosis* after showing symptoms of tuberculoid leprosy, or even between infection with *M. leprae* and the manifestation of the first leprosy

symptoms. The results of this survey are given in Table 11.

In young leprosy foci with a rather low tuberculosis index tuberculoid patients do indeed show a lower tuberculin index than healthy people of the same area. This difference is less evident in older leprosy foci, such as Wandamen Bay, with a high tuberculosis index. The difference between the percentages of negative P.P.D. reactions in the total of tuberculoid patients and the healthy people is statistically significant. Also the difference in the Mooi people alone is statistically significant ($P < 0.025$).

TABLE 11

Tuberculin Index in Healthy Adults and Adult Tuberculoid Patients from the Same Area

	<i>Healthy Adults</i>			<i>Tuberculoid Adults</i>		
	<i>No. Tested</i>	<i>No. Pos.</i>	<i>Tuberculin Index</i>	<i>No. Tested</i>	<i>No. Pos.</i>	<i>Tuberculin Index</i>
Mantembu	168	68	40.5	37	10	27.0
Mariadei	162	121	74.5	9	5	55.0
Wandamen	933	724	78.1	67	46	68.8
Mooi	243	113	46.5	37	9	24.3
Total	1,506	1,026	68.1	150	70	43.7

Discussion

CHAUSSINAND³ has put forward the hypothesis that an increase of tuberculosis is followed by a decrease in leprosy. Leprosy indices are highest in countries where the tuberculosis morbidity has not yet reached a high peak. Most articles speak about the leprosy index only. A relation between the tuberculosis index and the type of leprosy has not often been mentioned.

It is difficult to draw conclusions from these first surveys in New Guinea about the influence of tuberculosis on the incidence of lepromatous and borderline leprosy, since in many areas leprosy has been introduced recently, and probably also tuberculosis is a rather new disease, even in some coastal areas. It is not possible to trace the exact date of introduction of tuberculosis in these areas. A long follow-up period in some areas will be needed to evaluate the influence of tuberculosis on lepromatous leprosy.

The most important conclusion that may be drawn from this study is that a high relative susceptibility for tuberculoid leprosy goes along with a low tuberculosis index. The lower leprosy index in tuberculosis-rich areas at the coast may be explained by the hypothesis that previous tuberculosis contact prevents the development of a high percentage of tuberculoid lesions.

The development of the leprosy epidemic at Mantembu and other places, although less severe, does not differ essentially from the well

known epidemic at Nauru. There, the first "nodular" patient was seen in 1920. In 1923, 139 leprosy patients were found. After a history of 20 years a leprosy index of 350 per thousand was reached. From the isolated patients 68% were of the "macular" type. In 1929 BRAY⁴ reported that 90% of the cases were tuberculoid, mutilation being uncommon (minor tuberculoid variety), that in almost every family cases of leprosy were found, that the sex differentiation was negligible, and that 58% of the patients were older than 20 years at the onset of first symptoms (WADE⁵). Tuberculosis was rare then in Nauru.

DAVEY⁶ described the leprosy situation in tribes living "in conditions of relative isolation" in Nigeria. The leprosy index was high (121 per thousand), the type rate low (8.8%), and in 57% of the cases a single or only few tuberculoid macules were found. Tuberculosis was a rare disease in those areas. It was impossible to explain the epidemiology by the idea of intensive prolonged contact with lepromatous patients only.

Although probably more factors are involved, the following hypothesis explains a great deal of the findings. A newborn child has no effective immunity against leprosy (young babies do not react to lepromin).

How susceptible young children are can be learnt from the study of LARA⁷ at Culion. From the children born in the leprosarium, living in contact with their sick parents, 25% showed symptoms of leprosy before the age of five. However, in 85% of the cases spontaneous arrest of the disease was seen, and a long follow-up revealed that these children had permanent positive lepromin reaction. Probably these children were already potentially immune at birth, but the potential relative immunity had to be transformed into an effective immunity by contact with *M. leprae*.

The same process we may see in older patients with tuberculoid leprosy. At the onset the patient has no effective immunity against *M. leprae*. The leprosy bacillus has the opportunity to multiply. Visible lesions appear. In the meantime immunity develops, at first at the place where bacilli have multiplied, i.e. the central part of the tuberculoid macule. Later on the immunity is sufficiently advanced to stop further spread of the lesions and at the end the immunity may be strong enough to allow the patient to come in contact with lepromatous patients without danger of developing further symptoms of leprosy.

In young children the effective immunity is nil. However, most children possess a hereditary potential (relative) immunity, of a variable degree. Several factors may have influence on the transformation of this potential immunity into an effective immunity. The influence of non-pathogenic acid-fast bacilli is weak. *M. leprae* and *M. tuberculosis* are more effective. If the potential immunity is very

high, contact with acid-fast bacilli will produce a sufficient immunity to kill the bacilli in a very short time. If the potential immunity is not so high the bacilli will have time to multiply and visible lesions will appear. If such a child should come in contact with leprosy bacilli before he has contact with *M. tuberculosis*, leprosy symptoms of the self-healing tuberculoid type may appear. However, if he had tuberculosis contact before leprosy contact his potential immunity would already have been transformed into an effective immunity and no symptoms of leprosy would appear. A small number of children might have only minimal potential immunity or none at all, and in these children the disease would develop into a borderline or lepromatous type. Tuberculosis contact would not change this unfavourable condition.

In a community with much tuberculosis the number of adults who have reached the stage of sufficient effective immunity against *M. leprae* is much higher than the number of children. If leprosy is introduced in such a community only adults without sufficient potential immunity will contract a malignant type of leprosy and a minority with more potential immunity but who have not been in contact with *M. tuberculosis* will show symptoms of tuberculoid leprosy. In children the incidence of tuberculoid leprosy will be higher.

In a community with a few cases of tuberculosis the percentage of potential immune adults who have not reached the stage of effective immunity is almost as high as among children and many adults will show tuberculoid macules after introduction of leprosy. This seems to be the situation in the areas described in this article and at Nauru, West and Central Africa, etc.

From lepromin and tuberculin surveys⁸ we conclude that some individuals do not show a positive lepromin reaction, even after contact with different types of acid-fast bacilli, *M. tuberculosis* included. In other individuals the lepromin reaction remains so weak that some local resistance against *M. leprae* is possible, but this low immunity is insufficient to stop the disease (borderline leprosy). Probably these individuals lack a hereditary factor which is essential to enable the body to destroy the bacillus completely. If this hypothesis is right, there is no reason to expect that tuberculosis contact will change this condition and also nothing is to be expected from BCG vaccination. Only in individuals with a sufficiently high potential immunity will tuberculosis contact or BCG vaccination prevent the development of tuberculoid lesions.

It is still possible that BCG vaccination has some effect in individuals with a weak potential immunity. The possibility remains that a weak effective immunity is sufficient to destroy a small number of bacilli. If such a person has no repeated contact with lepromatous patients, he may be able to destroy incidental invasion of small

numbers of bacilli and remain free of leprosy. Furthermore, under conditions as described in this article, the effect of contact with tuberculosis and of BCG vaccination may influence the incidence of lepromatous and borderline leprosy indirectly.

In a susceptible environment, tuberculoid cases which are temporarily positive can act as a source of infection. When the incidence of tuberculoid leprosy is reduced by BCG vaccination, the chance that susceptible individuals come into contact with leprosy bacilli is also reduced, which may result in a decrease of new malignant cases of leprosy too.

In several of the areas described in this article we have noticed a spontaneous decrease in the evidence of new cases of tuberculoid leprosy, after the epidemic had reached a high peak. This may be explained by the fact that in every community there is a limited number of susceptible individuals. If the disease spreads fast, most individuals will soon have been in contact with leprosy. Those with a high potential immunity have shown nothing but a conversion of the Mitsuda reaction into positive; those with a lower potential immunity have shown tuberculoid leprosy; the few people without potential immunity show or will show lepromatous or borderline leprosy. The susceptible reservoir is soon exhausted and the incidence will decrease. Only some cases with a longer incubation period appear together with some cases in people who have escaped contact with the bacillus before. Only among the newborn children new susceptible individuals are found and the child index will rise. A second source of susceptible individuals is found in people who come into the community from the outside, by marriage etc. (BOENJAMIN⁹). The leprosy index will decrease and the type index will increase.

Of course, factors such as density of the population, hygiene, customs, segregation of patients, treatment, etc., play some role, different in each situation. However, these factors are probably of secondary importance. One has to consider the possibility that the decrease in the incidence of new cases at Nauru and in Africa was only partly the result of the anti-leprosy campaign and mainly the natural course of an epidemic in a susceptible environment.

In New Guinea this was certainly true, since a significant decrease was noticed before effective anti-leprosy measures had been taken. Measures, such as were taken at Nauru during the epidemic, in other countries failed to reduce the incidence of leprosy appreciably.

The question remains why the susceptible stock seems to be so different in many countries. This may be partly the effect of natural selection. From the genealogical point of view borderline and lepromatous patients are of major importance. In underdeveloped countries, but also elsewhere, before the sulphone period lepromatous patients had less opportunity of marrying than healthy people, especially when the disease started before adolescence and

was followed by mutilation or other severe symptoms. The average lifetime of married lepromatous patients was shorter than of healthy people. Advanced lepromatous leprosy may produce sterility in the male. In the poor condition of general health, the patients were less able to take good care of their children, which resulted in a higher death rate. The chance of abortion was increased in the female patient. These factors together result in a diminished offspring compared with healthy people. Thus after several generations the susceptible stock in a community may decrease. Although nowadays early treatment of cases, better social care, and a changed attitude towards the disease in most civilised countries have reduced the influence of these factors to a minimum, they are recent history and still operative in several countries where leprosy is endemic.

These conceptions have important practical consequences. It is not justifiable to base control measures on general statements such as the low infectivity of the bacillus, the low infectivity for adults, etc. It is not the *more or less infectivity of the bacillus which counts, but the susceptibility of the community*. Every anti-leprosy campaign must be based upon intensive and extensive local surveys, and study of the trends of leprosy in these areas. In some countries it may be quite unnecessary to insist on any segregation measures at all. In other countries early dispensary treatment, mobile treatment teams, leprosy villages, or some kind of relative segregation will be sufficient to produce a gradual decrease in the leprosy incidence. For such countries, therapy with a faster activity than sulphones may solve the leprosy problem in a short period.

However, susceptible communities give the choice of waiting till tuberculosis is widespread and the susceptible stock is reduced by natural means, or radical measures, including repeated intensive surveys, early voluntary segregation of all bacterially positive cases and BCG vaccination of all tuberculin-negative individuals. It is doubtful whether half-hearted measures which are relatively expensive are worth the cost. Besides, much social harm is done, without the balance of obvious benefit to the community. If segregation of the majority of patients living in contact with susceptible individuals is not possible for one reason or another in a very early stage of the disease and on a voluntary basis, it seems wise not to spend too much money on segregation of a minority of patients in a rather late stage of the disease, but to use the available funds for early case-finding, treatment, education, and BCG vaccination.

Summary

The history of leprosy in Netherlands New Guinea is described. In many parts of the country leprosy has been introduced only recently. The disease spread from the coast to the interior, and was studied from its introduction into the community in several tribes.

It was found that in tribes which have lived in relative isolation until recently leprosy follows a pattern which does not differ essentially from that described from Nauru, New Caledonia, and parts of Central and West Africa. This epidemiology has the following characteristics:

- (a) The disease spreads fast and the leprosy index becomes very high.
- (b) Most cases are of a mild minor tuberculoid type.
- (c) Cases are found in the majority of the houses in the village.
- (d) Adults are almost as susceptible as children.
- (e) Most patients did not have contact with lepromatous cases.

This epidemiological picture was found only in areas with a low tuberculin index. The differences in tuberculin index between these tribes and coastal tribes with a more common epidemiology were highly significant statistically, likewise in the tuberculin index of tuberculoid patients compared with healthy people from the same age group in the same area. The epidemiology is explained by the hypothesis that in people who possess a potential immunity against leprosy contact with tuberculosis produces an effective immunity, which prevents the development of tuberculoid leprosy symptoms in many people. It is improbable that tuberculosis contact gives any protection in people who do not have a sufficient potential immunity.

However, as some tuberculoid patients may act temporarily as a source of infection, it is possible that the reduction of the incidence of tuberculoid cases by tuberculosis contact or BCG vaccination may have an indirect effect on the incidence of lepromatous leprosy too. Therefore, although BCG vaccination does not guarantee individual protection against leprosy, it seems to be of definite value, especially in highly susceptible communities.

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AN ACCOUNT OF THE USE OF ETISUL IN THE TREATMENT OF LEPROSY IN THE NORTHERN REGION OF NIGERIA

by C. M. ROSS, O.B.E., M.B., D.T.M., C.P.H.
and J. F. TELFER, M.B., D.T.M. and D. D. HILTON, M.B., D.P.H.

Introduction: Material and Methods

In view of the favourable results of Etisul treatment reported by Davey and Hogerzeil (1959) we decided to investigate whether Etisul would be practical for use in outpatients by our trained auxiliary staff. We used Etisul by inunction on 38 patients during the period July to December 1959, comprising 18 outpatients at the Kaduna and Kano Area Clinics, 5 at the Zaria Provincial Leprosy Hospital, 6 at the Albarka Mission Leprosy Village, and 9 at the Katanga Native Authority Leprosy Treatment Village at Azare in Bauchi Province. We found that the treatment became popular and attendance was regular, except in one clinic. Etisul was supplied in unit dose tubes containing 5 g. of diethyl dithiolisophthalate in a suitable cream for percutaneous use, and we gave the inunction of the unit dose of 5 g. in three groups, namely twice weekly, thrice weekly, and daily. For children and young adults half the dose was given. The thrice weekly method seemed to us the most practical for our patients. With daily inunction the patient carried with him an unmistakable odour from the preparation and imparted this odour to his environment. There was little of this with the twice or thrice weekly inunction. We also noted that careless or inefficient inunction gave rise to body and environmental odour, which provided us with a very useful check on the thoroughness of the administration. At the beginning of the trial each patient was given a supply of weak Dettol, but this was soon found not to be necessary. The best sites for rapid absorption were the abdomen and chest, and about 20 minutes sufficed for the inunction.

Fall in Bacterial Index during Treatment

DAVEY and HOGERZEIL¹ and DAVEY^{2,4} describe the comparative speed of fall in the B.I. in patients treated with Etisul, as against treatment with other drugs. This decline was also noted in the patients in our trial. We used the method of estimating the Bacterial Index similar to that used in Uzuakoli of the Eastern Nigerian Leprosy Service, save that we differed in the number of smears taken and the sites of the body from which they were taken. We took smears from an ear lobe, a leprosy lesion, and the skin, and left out nasal smears as they presented difficulties. The average B.I. in the Kaduna and Kano group was 1.6 in June 1959 and 0.6 in December 1959. The Albarka group had an average of 2.0 in May and 0.8 in

December 1959. The Azare group declined from 3.5 in July to 0.8 in December 1959. We did not have a record of the B.I. in a control group, as most patients were selected because difficulty in treatment had been met with, or for the type of infection, or for complications of the disease. We noted morphological changes in *M. leprae* after 3 to 4 months of treatment, and decline in the number of bacilli showed itself first in the smears from the skin, to be followed by a reduction in the smears from actual leprosy lesions. The bacillary numerical reduction was very much slower in smears from the ear lobe and resolving nodules on the ear lobes, and in several cases these sites remained strongly positive persistently. These persistent cases were mainly new cases, who began with Etisul treatment alone or Etisul combined with DDS. This feature in several cases kept the overall B.I. from declining completely.

Results

On the whole the response was satisfactory. Patients became negative who previously had had 2 or 3 years of DDS treatment and yet persistently positive smears. Several young people of the Zaria and Albarka groups, who had early lepromatous macules or diffuse lepromatous infiltration, made a good response or became negative. A young female outpatient of the Kaduna group, who had indeterminate progressing to diffuse lepromatous leprosy, became negative and showed signs of resolution of the disease. The best bacteriological response was seen in cases established on regular DDS treatment.

Other satisfactory clinical results were seen in addition to the bacteriological changes. There were cases of marked resolution of peripheral nerve lesions and of improved state of the hands and feet. Furthermore, there were cases of malignant lepromatous leprosy who showed marked clinical improvement, with abatement of their lepromatous reaction (Erythema Nodosum Leprosum) and their progressive lepra fever.

Northern Nigeria is a large territory, with many races and tribal groups with different social customs, climatic conditions, and nutritional status. Variations can be expected in the incidence of lepromatous leprosy and in the deformity rate (Ross^a). These factors influence the mass treatment of leprosy and make it difficult. In the Azare District the leprosy populations show a marked susceptibility to involvement of peripheral nerves and to the malignant forms of leprosy.

Further Clinical Details: (a) Resolution under Etisul of Peripheral Nerve Complications (b) Resolution under Etisul of Lepromatous Lepra Reaction, Erythema Nodosum Leprosum, and Progressive Lepra Fever.

(a) Dr. Telfer of Azare General Hospital in Bauchi Province conducted the trial in the group at the Azare Treatment Village.

This village is the centre of a network of clinics attached to the Local Authority Dispensaries and the village gives temporary accommodation to patients who need specialised treatment. At the end of the Etisul trial Dr. Telfer remarked that he found the most convincing clinical sign of efficacious action by Etisul lay in the resolution in peripheral nerves, and lesions caused by their involvement. This opinion coincided with the findings in the other two groups.

Remarkable resolution of painful, tender, enlarged ulnar and peroneal nerves, and in swelling of hand and foot occurred in 7 Azare and 4 Albarka patients and 2 Kaduna outpatients. Minor degrees of contracture were corrected, and in the absence of joint fixation movement became normal and muscle tone was improved. One of the Kaduna outpatients, who was a female of 9 years with borderline leprosy, and the early stage of claw hand with minor degrees of contracture of digital and palmar tissue, showed correction of the hand condition at the end of treatment. The active movements became almost normal and there was great improvement in the muscle tone of forearm and hand.

In active lepromatous infiltration, with swelling and thickening of the joints and phalanges of the hands and feet, the danger of dislocation and bone injury was largely averted by the subsidence of the erythematous swellings of the subcutaneous tissues and subsidence of the pathological changes in the joints and thickened phalanges. The hands showed very great improvements in mobility and active movements in lepromatous cases without gross shortening of the fingers and disorganisation of the bones and joints of the hands.

(b) Difficulty in induction and maintenance of treatment by DDS caused the selection of three Azare patients and one Kaduna outpatient. Also the cases were selected for repeated reaction, persistent erythema nodosum leprosum, progressive lepra fever, and intolerance to any but minute doses of DDS which had prevented any response to therapy and caused deterioration of the patient's general condition and morale. Such patients had been given trial of other antileprosy drugs but with unsatisfactory results. The Azare patients were treated with Etisul alone, the Kaduna outpatients with small doses of DDS combined with Etisul. Intunction of the Etisul was thrice weekly. At the end of the trial there was resolution of the typical ruddy erythema (resembling an allergic urticaria) and resolution of the signs of progressive leprosy fever. There was a residual minor degree of erythema nodosum leprosum, without the typical severe associated symptoms. The patients had a sense of well-being and cheerfulness. In each case there was bacteriological and clinical improvement. The Kaduna patients were able to tolerate after four months a gradual increase of DDS dosage. A female aet. 12 years of the Azare group had a large sore on her elbow resembling a tuberculous lesion, with a septic dermatitis

possibly originating in a scabies infection, and both these conditions resolved during Etisul treatment.

Side Effects

There were two patients, both of borderline type, who had a localised reaction in their lesions, which became erythematous and swollen, but this quickly subsided on suspending treatment and no harmful result followed the reaction.

Summary

1. We tried Etisul as a treatment in 38 patients, both outpatients and a few inpatients, in separated regions of Northern Nigeria, and excellent results were obtained, the administration in inunction clinics being well within the competence of trained auxiliary leprosy workers. The period of the trial was July to December 1959. Clinical improvement was good, and the Bacterial Index fell markedly, viz. 1.6 to 0.6 in one group, 2.0 to 0.8 in another group, 3.5 to 0.8 in a third group.

2. Etisul has a useful and practical part to play, even in outpatient treatment. In countries like Northern Nigeria, where there is a high endemic rate of leprosy, the rapid decline under Etisul of the Bacterial Index of bacilliferous cases is of vital importance to the control of leprosy.

3. With Etisul hope begins to appear for the satisfactory treatment of the malignant forms of leprosy, such as show intolerance to standard treatment. With the help of Etisul there may be attained a gradual induction of standard treatment and a possible decline of the Bacterial Index in a comparatively short time. We need further trials of Etisul to explore the possibility of corticosteroids being replaced by Etisul in the treatment of these malignant forms.

4. We found resolution of peripheral nerve involvement and its concomitant lesions, with favourable results on active movements of the small joints of the hands and feet and muscle action of the limbs, so that joint fixation and tissue contracture and impairment of muscle function are all rendered avoidable.

5. We think that deformity may be prevented under the influence of Etisul by the early resolution of lepromatous pathological conditions affecting bone and joint tissue of the hands and feet. We observed an Etisul action which is quite specific in clearing up swollen hands and joints and in preventing thereby the progressive shortening and disorganisation of the hands and feet.

6. We found that when the patient cooperates and makes effort in the thorough inunction required for Etisul, he gets the benefit of valuable additional exercises and movements, as well as elevation of morale.

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THE USE OF "ETISUL"
(DIETHYL-DITHIOLISOPHTHALATE)
IN THE TREATMENT OF
LEPROSY IN AFRICANS

by M. F. LECHAT

Yonda Leprosarium, Coquilhatville, Belgian Congo.

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Stimulated by the work of Davey in Nigeria, we carried out a trial of diethyl-dithiolisophthalate ("Etisul") cream in in-patients at the Yonda Leprosarium.

The immediate aim of this first trial was not to determine the therapeutic efficacy of the drug, but to assess its local tolerance in Africans. The clinical and bacteriological progress of the patients was only recorded incidentally.

1. History

Del Pianto must be credited with having drawn attention, in 1950, to the fact that a mixture of two mercaptans, i.e. mercaptobenzo-thiazol-5-sodium sulphonate and ethylthiosulphate, inhibits the development of tuberculosis in infected guinea-pigs.

After various authors (Brown, Solotorovsky, Mathewson, Chang, etc.) had carried out numerous investigations into the action of various mercaptans in tubercular infections in mice, in infections with *Mycobacterium leprae*, and in human tuberculosis, Davies discovered diethyl-dithiolisophthalate (ETIP, ET, "Etisul", Ditophal). The review by Chang and Doull (1959) of the development of these investigations should be consulted for details.

As regards human leprosy, Bertaccini in 1957 treated 37 lepromatous cases with ethyl thiosulphate *by mouth*, in a dosage of 0.8-1.6/g.day, for a maximum of nine months, with interesting results.

Davey in Nigeria used diethyl-dithiolisophthalate in the form of a cream ("Etisul"). At the Tokyo Congress he showed photographs of patients treated with this drug and reported having obtained remarkable improvement with it. In two recent papers he reported the results achieved in 133 patients. The most outstanding aspect was a spectacular drop in the bacterial index: in certain groups of patients studied by Davey this fell by half in 4, 8 and 12 weeks, respectively.

"Etisul" shows remarkable activity, particularly in fresh cases. "Etisul" is thus of interest only in the early stages of treatment. In older cases, where scanty bacilli persist after several years of treatment (with other drugs), it is said to be ineffective.

When it is used alone, its effect subsides after two or three months. We do not yet know whether and under what conditions the drug may recover its efficacy, when a second course is applied. Combination with parent sulphone is highly effective, but where the two products are administered together from the beginning, i.e. where the maintenance dose of DDS has not yet been reached by the time the action of "Etisul" has subsided, the emergence of resistance cannot be prevented. Starting the parent sulphone some weeks in advance, on the other hand—and this is of particular importance—decidedly prevents the appearance of such resistance. It is said that the same results can also be obtained by beginning with three types of treatment, i.e. "Etisul", DDS and DPT, simultaneously. In this case DPT, in a daily dosage of 2 g., is intended to prevent resistance from emerging towards the third month, while waiting for the standard dose of DDS to be attained.

2. Choice of Patients and Method of Administration

It seemed as if the odour of "Etisul", generally considered as extremely unpleasant, might present a major obstacle to its extensive use.

The object of our trial was to study the acceptance of this new type of product by African patients.

We chose 28 patients, all males, including two children. 26 were of the lepromatous type, including eight fresh cases and had never previously received organised treatment, one reactional tuberculoid case and one borderline case. Four subjects did not finish the treatment: two of these experienced a severe lepra reaction (one with oedema of the hands and one a straightforward reaction, without erythema nodosum), and two left the leprosarium.

"Etisul" was administered for a period of 8 to 15 weeks, twice weekly to seven of the subjects, and three times weekly to the remainder, in a dosage of one tube (=3 g. of the drug) per session.

Following the advice of Davey, who had noted that application of the cream to the legs was without effect, we caused the product to be massaged into the skin of the back, over a wide area extending from the belt to the shoulders. This type of application is rapid and requires no nursing personnel. The patients are arranged in a circle, either sitting on stools or, better, standing up, each massaging the back of the one in front of him, and the first member of the group massaging the back of the last. The patients spontaneously took up the habit of singing a work song during inunction sessions, which seems to encourage them. The advantage of this method lies in the fact that each patient demands to be massaged as vigorously by the one behind him as he is massaging the one in front of him.

Each session lasts 20 minutes. In spite of vigorous massage, the back is still covered with cream at the end of that period. The patient

then waits 2–3 hours before covering his back, attends to his jobs and then has a wash.

Care is necessary in ensuring that patients, particularly children, do not wash as soon as the drug has been applied.

3. Local Tolerance

Cooperation by the patients was excellent.

By not using any constraint on those treated with “Etisul”, by not threatening penalties against those who might shirk the treatment, and by simply stating that this is a costly and probably very effective drug, we obtained an attendance of 90.5% at the sessions, a proportion which is usual at the beginning of any new therapeutic trial, but is only exceptionally seen to persist for several months, as in this case. In our group this level of attendance was kept up until the end of the course.

While this trial was in progress, many patients asked to be treated with “Etisul”, and these were invariably men. Up to the present we have not succeeded in persuading women to let themselves be inuncted, since, due to the shortage of covered accommodation, the sessions take place in the open air and the women absolutely reject any attempt to convince them.

Contrary to our initial fears, the odour of the product, either when applied to the skin or when excreted via the lungs, did not give rise to any objection. Not a single complaint was made either by the patient himself or by those surrounding him. According to those involved, only the first two sessions are objectionable, and then they become used to it.

We questioned the treated patients both separately and as a group, and some of them, being former clerks, policemen, etc. did let us have a little report. Some of these have certain jobs in the leprosarium, such as: teacher of French in the social centre, registrar in charge of administrative reports, foreman carpenter, lorry driver, etc.; it seems that they prefer to avoid coming into contact with the public on the evening after their inunction with “Etisul” (the sessions took place about 3 p.m.), but they all feel that, if they were to be treated with this cream on an out-patient basis, they could all go back to their work the next morning without any difficulty. On several occasions, when we were receiving visitors shortly after an “Etisul” session, we had cause to call in our shorthand typist, who was receiving the drug and who still had his back bare and covered with cream, in order to give him some task or other. While it is true that the odour was powerful, we never heard the slightest remark from the visitors. The odour of “Etisul” is certainly much less disagreeable than that of certain chaulmoogra esters, which was at one time a feature of any leprosarium, and which still persists today in certain buildings.

The reason for our discussing this subject at length is that the odour of the product is at present a subject for comment and is often considered to be an obstacle to its use.

Two complaints, on the other hand, were expressed by almost all the patients:

1. Excretion in the sweat.—Wherever heavy physical work is involved, the sweat, for at least two days after an “Etisul” inunction, carries a marked odour of the drug and imparts it to the clothing. As regards the laundering of the latter, they can be washed with other clothing without transmitting the odour to it. The patients, however, said categorically that certain soaps immediately remove the odour from the clothing, while others are without effect. The same remark applies to the bath they take after inunction. No more detailed information could be obtained from them.
2. Odour from the soil and withering of grass after contamination with “Etisul”.—In the beginning the patients used to wash behind their houses, after having rolled in the grass for the purpose of rubbing their back, which was still covered with cream. Some hours later the grass appeared withered, and the soil upon which the washing water had been emptied gave off the typical odour for several days, particularly after each rainfall.

A last point regarding this odour: we became forced to store “Etisul” in a separate place outside the hospital, since the cardboard boxes containing the tubes were not airtight.

To sum up: we do not believe that the odour of “Etisul” presents an obstacle to its use in Africans. Some easy precautions are all that is required, and it is as well not to dwell excessively on this problem. The odour is certainly less unpleasant for the patients than that of chaulmoogra and that of vitamin B complex, both of which either have been, or are still being, extensively used in leprosaria.

At present we are testing the tolerance of “Etisul” on an out-patient basis in intelligent patients.

4. Results of Treatment

As a secondary consideration we studied the progress of patients treated with “Etisul”. Naturally our results, which were obtained in a small number of leprosy patients, lack any statistical value.

It is, however, of interest to compare them with those published by Davey, and we feel they are worth recording.

We have divided the patients into two groups, according to the time at which treatment was begun.

A.—First Group (March 1959)

Seven patients were chosen, including:

- (a) Four severe fresh lepromatous cases (two of them children)

and one adult borderline case, all previously treated with sulphones for 1 to 7 months.

(b) Two severe lepromatous patients, who had started "Diasone" treatment in 1949, had disappeared in 1951, and had remained without treatment until they were re-admitted in 1956 and 1958, respectively; at that time the patients presented with very severe and florid lepromatous leprosy, with generalised infiltrations and lepromata. At the time they were incorporated into the "Etisul" group they had been receiving DDS for 29 and 3 months, respectively.

The nature of the skin lesions in the lepromatous patients can be summarised as follows:—

<i>Patient No.</i>	<i>Lepromata</i>	<i>Infiltration</i>	<i>Macules</i>	<i>Previous Reactions</i>
M.L. 0937	+	+	—	in 1957
N.C. 1350	+	+	—	—
L.G. 2899	—	+	—	—
A.J. 2904	+	+	—	—
I.P. 2914	+	—	—	—
E.E. 2921	+	+	+	—

Clearly, these patients were selected, since all but one were either fresh or relapsing lepromatous cases. They were not chosen by virtue of any possible intolerance to sulphones or of any lack of improvement with ordinary treatment.

"Etisul" cream was administered twice weekly and later, during the last two weeks of the course, three times weekly, at the rate of one tube per session per adult patient, and half a tube in children, which was vigorously massaged into the skin of the back for 20 minutes (the first application consisted of one tube for five patients).

All patients were treated simultaneously with DDS tablets in a dosage rising from 400 to 600 mg. of parent sulphone per week, given in three parts.

<i>Patient No.</i>	<i>Duration of Treatment (weeks)</i>	<i>Total Dose of "Etisul" (tubes)</i>	<i>Total Dose of DDS (during "Etisul" treatment)</i>
M.L. 0397	12	27.5	6.70
N.C. 1350	14	32.2	6.90
L.G. 2899	12	14.5	Regular, but record lost at school (child)
A.J. 2904	14	32.2	6.80
K.J. 2910	14	32.2	6.80
I.P. 2914	14	31.2	8.50
E.E.2921	14	16.2	1.45 (child)

The following is a brief summary of the clinical results in each case:—

1. **0937—M.L.:** Numerous lobster-shell-like infiltrations over the whole body.
1.4.1959 Lepromata still persist on the ears, chin and forehead, but have clearly shrunk as a result of two years' sulphone treatment. Diffuse coarsening of the face.
8.6.1959 Infiltrations flattened and scarring; lepromata flattened; coarsening of the face reduced.
2. **1350—N.C.** Generalised infiltration over the whole body; confluent lepromata on the ears; nasal fossae blocked.
10.2.1959
8.6.1959 Continues to show infiltrations and lepromata, but these are smaller and less turgid; nasal fossae patent.
3. **2899—L.G.** Pigmy child showing diffuse coarsening of the face, some beginnings of infiltration, and markedly coarsened ears.
1.4.1959
8.6.1959 Coarsening reduced, but infiltration persists, with shiny appearance of skin; lepromata flattened, almost scarring.
4. **2904—A.G.** Beginnings of infiltration on the chest, back and arms; clusters of small lepromata on face and ears; nasal fossae blocked.
20.2.1959
8.6.1959 Slight infiltration persists on the chest, back and arms. The lepromata have completely cleared up, except on the ears where they are much reduced in size; nasal fossae patent.
5. **2910—A.J.** Previous clinical course unknown. Shows numerous borderline macules over the whole body, including two on the left arm and abdomen, having some micropapules near their borders, which are slightly raised and show a deeper copper colouring at that level.
20.2.1959
8.6.1959 No change from the first examination.
6. **2914—I.P.** Very slight incipient infiltration on the chest; thick and florid lepromata on the upper lip, chin, ears, extensor aspects of the arms, and back.
8.6.1959 A very slight infiltration persists on the arms and the chest; all lepromata have disappeared without trace.
7. **2921—E.E.** Incipient lepromata on the ears, diffuse coarsening of the face, tawny macules of greasy and infiltrated appearance on the back.
8.6.1959 Lepromata, infiltrations, coarsening and macules have disappeared without trace.

For bacteriological purposes biopsies were obtained at the beginning, during and at the end of the treatment from six different sites: apparently healthy skin, skin of forehead and chin, apparent infiltration or macule, ear lobes and nasal mucus (scrapings).

The tests were carried out by a laboratory technician who had no access to clinical data that might have influenced his findings.

In order to illustrate the progress we calculated the bacteriological index according to Davey's method, allocating a coefficient ranging from 1 to 4, according to the density of the bacilli for each sampling site, grouped for all sites and then divided by the number of biopsies. We did, however, take six biopsies instead of four and calculated no average, contenting ourselves to add the various coefficients together, thus obtaining a maximum of 24.

We are listing below the results obtained in the most representative patients, compared with those obtained in lepromatous patients who were chosen at random from those presenting the same bacteriological index.

<i>Patient No.</i>	<i>"Etisul" Treatment</i>	
	<i>Onset</i>	<i>End</i>
1350	16	10
Control	16	14
2904	14	8
Control	14	10
2914	20	6
Control	20	16
2921	18	5
Control	18	16

Patients not shown above were not excluded because their results differed, but as a result of discrepancies between the dates of the biopsies, as between controls and treated subjects, the reason being that patients are highly reluctant to undergo repeated biopsies.

Biopsies taken three months after the end of "Etisul" treatment, when patients had continued to take DDS in a dosage of 600 mg. per week, indicate that the bacteriological improvement still persists.

B.—Second Group (June 1959)

Among 21 patients chosen, four were excluded (by reason of either departure or lepra reaction), two were added to the group during treatment and will not be considered here, since their period of observation was too short. Two patients were residual lepromatous cases with very marked lesions, with scanty bacilli appearing only intermittently.

Here we are concerned only with the 13 patients showing bacilli, including 12 lepromatous cases and one with a reactional tuberculoid form.

Remarkable clinical progress was made by all the lepromatous cases: the lepromata resolved and infiltrations were clearly reduced to scar proportions. This progress was followed by means of clinical photography and biopsies.

We feel the bacteriological progress is interesting (see Table).

Eleven of these patients were treated with "Etisul" plus DDS in a dosage of 600 mg. per week. Four received only "Etisul" (these are marked + in the Table).

The fluctuations in the bacteriological index from one week to the next are of no importance, since the bacilli are not distributed uniformly throughout the skin, and it is clearly impossible always to take a biopsy from exactly the same spot,

Bacteriological Progress

	<i>Weeks of "Etisul" Treatment</i>																
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
1349+	13	—	—	5	2	3	3	9	4	4	—	4	3	3	2	5	—
1395+	7	—	—	5	2	2	2	—	1	2	—	2	—	2	—	1	—
1920+	8	—	—	3	2	2	2	—	2	4	—	2	2	0	—	0	—
2003	14	—	—	—	—	5	7	2	—	—	3	2	5	—	3	—	—
2463	—	5	—	—	5	4	2	1	4	2	1	—	—	—	1	5	6
2591+	6	—	—	2	1	1	1	1	0	—	—	0	—	0	—	0	—
2744	—	—	6	—	—	3	4	1	0	—	2	—	1	5	4	—	—
2795	7	—	—	2	2	2	0	1	0	—	—	—	2	0	0	1	—
2875	14	—	—	4	—	2	3	3	1	0	—	1	0	3	1	4	—
2882	6	—	—	2	2	1	3	2	1	1	—	2	1	2	4	3	—
2884	11	—	—	—	2	1	1	4	0	2	—	0	0	2	1	1	—
2888	7	—	—	2	3	—	—	2	2	0	—	—	2	3	—	—	—
2925	8	—	—	5	8	1	—	3	1	2	—	1	2	2	0	1	—

Be that as it may, it seems that the changes produced by "Etisul" in the bacteriological index of leprosy patients are, at worst, unexpected and out of the ordinary.

Our results are comparable with those obtained by Davey in the groups he designated as 1A (9 cases) and Cb (14 cases). It should be noted, however, that, judging by the bacteriological index, the patients studied by Davey appear to have had a more severe stage of the disease. Actually, our bacteriological index tends to be lower, overall, than that of Davey, due to the fact that we introduced in our series two additional biopsies (six instead of the four carried out by Davey), which were taken from sites that generally become negative right at the beginning of sulphone treatment (apparently healthy skin and skin of the forehead).

It would be of great interest to compare these results with those obtained by using sulphones alone. But the progress of each patient, whether treated with sulphones or not, varies too greatly, and the error inherent in repeated bacteriological examinations is too high, to allow us to set much store by such a comparison. We might confine ourselves to noting that such a rapid fall in the bacteriological index is only exceptionally seen in patients treated with DDS, particularly at a time when, after marked improvement during the first two years of treatment, the bacteriological index becomes stable and often remains at the same level without marked fluctuations for several years.

5. Conclusions

In the form of cream ("Etisul") diethyl-dithiolisophthalate is fully accepted by African patients, is perfectly tolerated topically, and its slight odour does not form an obstacle to its use.

Lepromata are resolved with such speed that a patient with lepromata and infiltrations may fail to present any visible lesions after two months' treatment. This improvement is maintained wherever the patient is changed over to final treatment with sulphones.

The most remarkable aspect of the drug is its effect on *M. leprae*. In the majority of patients who show bacilli, the bacteriological index drops in the space of a few weeks; it may even happen that the patient suddenly becomes bacteriologically negative while still presenting clinical lesions.

The small number of patients studied here does not allow statistical conclusions to be drawn, but the individual results obtained, which are hardly ever seen at all in our sulphone-treated patients, can be regarded as really surprising.

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PRELIMINARY TRIAL OF ETISUL IN THE TREATMENT OF LEPROSY

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Compound 15.688 of ICI, which is now known as diethyl dithiolisophthalate, ETIP or Etisul, was found to be extremely active against tuberculous infection in mouse and guinea pig (Davies and Driver 1957)¹. It was also observed that when the drug was rubbed into the skin it was capable of exerting a chemotherapeutic effect in experimental tuberculosis in mice (ethyl mercaptan is considered to be released in the body after inunction of Etisul). Davies and Driver² (1958) studied the effect of ethyl mercaptan itself on intracellular tubercle bacilli. Using a modification of Suter's method, *M. tuberculosis* was grown in guinea pig monocytes and human monocytes where it was found to be effective.

The first clinical report was published by Davey^{3,4} (1959) where he concluded that patients differ widely in the response of their infection to this drug but a dose of 3 to 6 c.c. inuncted twice weekly has been found in some patients to exert a powerful chemotherapeutic effect on the bacilli not only at the site of inunction but generally throughout the body. The chemotherapeutic effect, though powerful, is short lived, as drug resistance developed after three months. Hence it is better to give Etisul in the beginning of treatment along with a standard antileprosy drug such as DDS.

Method and Materials

Three lepromatous cases were selected for this trial and took treatment for the last six months. Previously they did not take any treatment for their skin condition and reported first to this department as fresh cases. Detailed clinical, bacteriological, immunological and histopathological study was made. Photographs were also taken. Repeated clinical examinations were made once a week and bacteriological examinations were made once a fortnight.

Etisul is a cream for inunction. In addition to diethyl dithiolisophthalate it contains also a specially scented perfume to mask the garlicky odour.

2.5 g. of Etisul was rubbed on alternate days over the right arm and right forearm of the patients but after the fifth application there developed papular and erythematous lesions over the right forearm in one case. The drug was then stopped for a few days and calamine lotion was applied. Later 5 g. was rubbed twice weekly over a large non-hairy area in addition to right arm and right forearm. An

unpleasant odour was evident during the time of application and also later through the breath.

Result

Clinically there was no improvement noticeable in any patient during this six months' trial. In spite of continuous regular treatment the clinical condition gradually deteriorated. The lesions became thicker and more erythematous. Infiltration became more extensive. Swelling of the feet and leg developed in one patient and of the hands in another. In one patient eye lesions became more extensive. No improvement was noticed on bacteriological examination. Instead of diminution of the bacteriological index, it increased gradually. Morphologically no demonstrable change in bacilli was noticeable in any case.

Table showing Result of Treatment with Etisul

<i>Serial No.</i>	<i>Name, Age, Sex</i>	<i>Type</i>	<i>Lepro-min Test</i>	<i>Initial B.I.</i>	<i>Present B.I.</i>	<i>Clinical Improvement</i>
1.	P.B. 40 yrs. H.M.	L2-3	Neg	2.0	3.2	The lesions became more extensive and thicker and redder. A few nodules and swelling of the hands developed.
2.	F.R. 35 yrs. M.M.	L2-3	Neg	2.0	3.0	The lesions became more extensive. No restoration of the sensation lost.
3.	M.R.S. 55 yrs. H.M.	L2	Neg	2.3	3.1	Eye lesions developed. Swelling of the feet and leg started.

Discussion

It was observed by Davey that the drug may be effective in some cases and may not be so in some others. The reason is not yet known. Davey also observed that in his own series, no appreciable improvement was observed in some cases after three months or so. But it was found effective when administered along with any antileprotic drug. In our small series, no change in the number or morphology of bacilli was found during this period of six months. He found rapid decline of B.I. in a few cases within three months. However, this was not maintained subsequently unless standard drugs were added in good time.

Conclusion

During this six months' trial with this drug alone, no appreciable improvement was noticed, under a method which began with a limited inunction over the right arm and forearm.

Summary

Three active lepromatous cases were treated unsuccessfully with Etisul alone.

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2. DAVIES, G. E. and DRIVER, G. W. (1958) *Nature*, **182**, 4936, 644-665.
3. DAVEY, T. F. and HOGERZEIL, L. M. (1959) *Leprosy Review*, **30**, 61 & 141-152.
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RUSSIAN PAPERS ON LEPROSY

Dr. J. R. INNES, *General Secretary-Treasurer,
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(Paper delivered at the Symposium on Leprosy Research, London, 20.6.60)

Introduction

Prof. N. A. Torsuev of Rostov on Don has kindly made available 25 printed copies of his Bibliography, which I have translated from the Russian into English and is in your hands, both in the original and in translation, so far as the limited number of original copies will permit. Prof. Torsuev requests that exchange of literature may please be set up with him, from those receiving the Russian Bibliography, and any interested workers. Prof. Torsuev has also kindly sent me a personal communication, giving his own account and his own assessment of the Russian literature, which is of such interest that I first give in this paper his remarks (in my translation.)

N. A. Torsuev on Russian Leprosy Work

Prof. Torsuev writes as follows:—

Soviet leprologists have published more than 1,200 scientific papers, nearly as much as for the whole pre-revolutionary period, and anti-leprosy organisations have edited more than 20 collections of papers and many monographs. Since 1957 there has been periodical issue of "Scientific Notes of the Leprosy Research Institute". The monographs deal with different problems of leprosy, such as;

I. M. BURAKOV (1938) "Clinical and Histopathological Changes in the Nose, Throat, and Ear in Leprosy."

G. I. ZHIVATOVSKII (1938) "The X-ray Picture of Bone Changes in Leprosy."

I. M. KRUKOVER and N. V. GOLDFARB (1936). "The Upper Respiratory Tract and Organs of Hearing in Leprosy."

L. I. KOSOLAPKINA (1943) "Histopathology of Leprosy Lesions."

G. S. KULESHA and I. M. MALININ (1929). "Data on the Study of Leprosy in Kuban".

MELEK BEK SULTANOV (1928) "The Study of Leprotic Dermal Histological Changes, and the Histogenesis of Leproma."

A. N. MIRAYANTS (1934) "Leprosy in Armenia."

N. M. PAVLOV (1934) "Ocular Leprosy."

A. M. FALKOVICH (1939) "Oral Leprosy." *and others.*

In 1951 and 1952, N. A. Torsuev published two issues of his monograph "Leprosy", and in 1957 "Collective Guide on the Knowledge and Prophylaxis of Leprosy".

The U.S.S.R. has two scientific grades, namely "Candidat" and "Doctor of Medical Sciences", which are given after a public

defence of the appropriate theses, which must be of high quality. There are more than 50 such dissertations on leprology.

A great part of the published work is devoted to the problem of the organisation of measures to fight leprosy, the form and methods of prophylaxis, and to the study of epidemiological problems. Soviet authors are particularly interested in social and economic factors. In the epidemiology of leprosy the campaign used to be influenced by the idea of isolation of the patient and of treatment in a leprosarium. Now it is based on the dispensary, with all medical and preventive organisations of the Public Health Department working with the dispensaries. In the dermato-venereological dispensaries in the endemic zones, doctors are chosen to take charge of the anti-leprosy work, with registration of the patients and their relatives, periodical medical examinations, the arranging of dispensary treatment of patients discharged from leprosaria, mass inspections and examinations of the people in dangerously infected areas.

V. I. Kedrovskii has done special work in the microbiology of leprosy and thinks that in an artificial medium the causal organism could transform itself into a more complicated micro-organism of the type of *Actinomyces* or *Streptothrix*. There have been several studies of this kind. In 1931, A. A. Shtein and M. I. Tzheperin noted in the lepromin inoculation site the early allergic reaction which was described several years later by J. M. M. Fernandez. A. A. Maximova showed the possibility of modifying the reaction in lepromatous by a repeated intradermal injection of rat leproma (*M. lepraemurium*). There was a positive Mitsuda when regular lepromin was injected.

I. I. Perevodchikov made a deep study of the reaction of leprosy patients to different pharmaco-dynamic tests. N. A. Chernogubov and N. F. Pavlov (1925) were the first to describe Lichen Leprosus.

N. A. Torsuev (1947) described the leprosy reaction, similar to that of dermatitis herpetiformis Dühring.

G. N. Peshkovskii proved the higher excitability of the sympathetic nervous system in leprosy patients.

A. V. Minaev showed changes in chronaxy, even in parts of the skin apparently clinically healthy.

N. I. Fedorov and others developed the study of nerve symptoms in leprosy.

S. N. Rudchenko and K. I. Vorobieva studied the clinical features of tuberculoid leprosy.

I. F. Alieva described acute and chronic vaginitis of leprosy.

I. I. Nazarov used biomicroscopy to prove the presence of pathological changes in clinically healthy eyes of lepromatous patients, and atrophy and partial destruction in the iris of tuberculoid patients.

Soviet leprologists, I. N. Alamdarov, I. N. Ermakova, N. A. Ivanova, A. I. Kartamishev, L. I. Kosolapkina, N. A. Torsuev, A. A.

Shtein, and others described the histo-morphological changes in affected nerves and in the apparently healthy skin, fine changes in the carotid sinus, a degenerative process in nerve tissues in autonomic ganglia, the over-compensated growth of the synapses in the aorta, and in the spinal cord ganglia and sympathetic and parasympathetic ganglia; they also showed the condition of the basic argentophilic tissue and expounded the histopathology of the reactive phases of leprosy, and studied different visceral organs. As aid to the diagnosis of early imperceptible skin lesions, N. F. Pavlov described the method of intravenous injection of 6.0 to 10.0 ml. of 1% solution of nicotinic acid.

A lot of work has been done on therapy, which in the USSR is based on the principle of "individualization of the complexes", and on combined treatment.

In 1959 Prof. N. A. Torsuev compiled and edited "Bibliograficheskii Ukazatel Rabot Otechestvennikh Avtorov po Lepre (Bibliographical Index of Papers by Russian Authors, up to the year 1957 inclusive).

Analysis of the Bibliography

(The above represents the translation of the remarks sent by Prof. Torsuev. Here follows a beginning of an analysis of the papers.)

The Bibliography contains in Section 1 the titles of 1975 papers in Russian. Section 2 contains titles of 664 papers in languages other than Russian.

Allergy and Immunity: 14 papers.

Bibliography: 5 papers

Biography and Obituary: 20 papers.

Biochemistry: 37 papers.

The Antileprosy Campaign: 184 papers.

Upper Respiratory Tract: 55 papers.

Internal Organs: 33 papers.

Geography and Statistics—

Russian Empire and Soviet Union	15 papers
Azerbaijan Republic	11 papers.
Armenian Republic	13 papers.
Belorussian Republic	3 papers.
Gruzinsk Republic	6 papers.
Kazan Republic	6 papers.
Latvian Republic...	6 papers.
Prebaltic Republic	34 papers.
Russian Soviet Federated Socialist Republics	165 papers.

Carry forward 259 papers.

			Brought forward	259 papers.
	Tadzhik Republic	6 papers.
	Turkmen Republic	10 papers.
	Uzbek Republic	20 papers.
	Ukraine Republic	17 papers.
??	Finlandia	14 papers.
	Estonia	26 papers.
	Other Regions	30 papers.
				<hr/>
				382 papers.
Histopathology—				
	general	46 papers.
	of skin	37 papers.
	of nerves (peripheral and central nervous system)	47
				<hr/>
				130 papers.

The Eyes: 73 papers.

Diagnosis (Definitive and Differential): 104 papers.

Dissertations of the Soviet Period, for Doctor: 8; for Candidat, 85.

Recovery and Relapse: 17 papers.

History: 70 papers.

Case Histories (see Geography and Statistics): 275 papers.

Classification and Nomenclature: 17 papers.

Bones and Joints: 27 papers.

Blood: 55 papers.

Cultures: 34 papers.

Leprosy and Syringomyelia: 17 papers.

Leprosy and Tuberculosis: 10 papers.

Leprosy and Other Infections: 12 papers.

Lepromin Test: 21 papers.

Leprosaria: 174 papers.

Lepromatous Type (see Case Histories): 36 papers.

Lepromatous Reaction: 24 papers.

Treatment—

general: 72 papers.

hormone preparations: 3 papers.

with "R.D.": 32 papers.

Immunotherapy: 35 papers.

local: 16 papers.

of Reactions: 4 papers.

of Diverse Kinds: 115 papers.

with Sulphones: 36 papers.

Surgical: 5 papers.

Physiotherapy and Orthopaedics: 29 papers.

Treatment with Phthivazid: 6 papers.

Treatment with Chaulmoogra: 37 papers.

Total No. of Treatment Papers—390.

Microbiology: 62 papers.

Nerve Symptoms: 65 papers.

General Pathology and Pathogenesis: 53 papers.

Antileprosy Campaign Societies: 68 papers.

Official Data: 34 papers.

Leprotic Pemphigus: 3 papers.

Sexual System: 13 papers.

Popular Literature: 13 papers.

Rat Leprosy: 41 papers.

Prophylactic Measures: 29 papers.

Various: 29 papers.

The Mouth: 8 papers.

Directives and Articles of General Nature: 23 papers.

Symposia, Papers, Bulletins: 19 papers.

Cardiovascular System: 10 papers.

Serology: 52 papers.

Conferences, Sessions, Congresses: 32 papers.

Transformation of one Type of the Disease to Another: 10 papers.

Tuberculoid Type (see Case Histories): 21 papers.

Tuberculoid Reactions: 7 papers.

Experimental Leprosy: 38 papers.

Epidemiology: 106 papers.

FACTORS ASSOCIATED WITH REACTIONAL STATES IN LEPROSY WITH SPECIAL REFERENCE TO MALARIA

by R. E. PFALTZGRAFF, M.D., *Garkida Leprosarium, N. Nigeria*

During several years of treating patients with leprosy we noticed an apparent relationship between intercurrent disease and the occurrence of reactional states. Since there seems to be very little reference to this relationship in the literature, we attempted a statistical analysis of this relationship by examining all the instances of recorded reactions occurring in the patients in the Garkida Leprosarium during the eight-year period beginning 1st January, 1951. The census of patients under care varied considerably during these years (see appended Table). The fluctuation was chiefly in milder cases, and the total number of severe tuberculoid, dimorphous and lepromatous cases, namely those who would be likely to suffer reactions, would not have been significantly different in the various years.

In this study all reactional conditions presumed to be associated with leprosy were included in the records; thus including lepra reaction, erythema nodosum leprosum, neuritis, iritis, etc. All attendances at the dispensary for reactional states were recorded except where a patient complained more than once in a month, when it was presumed that it may have been the same reaction. However, if a patient called again in a succeeding month he was counted again. Thus for a continuous reactional state a patient would be counted once monthly until cessation of the reaction.

It will be noted in the Table that there is an increase of reactions during the times when there have been epidemics of chickenpox and measles, as well as during the month in which a large number of the patients were immunized against smallpox and developed vaccinia¹.

The most significant of our findings is the marked increase in the number of reactions coming on during the rainy season which occurs here during the months of July, August and September. The incidence of malaria is also highest during these months and October. Thus it was postulated that perhaps the malaria was a precipitating factor in reactional states, and we decided to determine the effect of malarial suppression using pyrimethamine (Daraprim) 25 mgm. weekly during the months of July, August and September, during 1955, 1956 and 1957. This caused an immediate drop in the number of reactions per month during the time of year when they had previously been the highest². In 1958 no malarial suppression was attempted, and the number of reactions per month again rose during the months of high malarial prevalence.

INCIDENCE OF REACTIONAL STATES IN LEPROSY

YEAR <i>Number of Patients under therapy during year.</i>	1951	1952	1953	1954	1955	1956	1957	1958	<i>Total Reactions</i>	<i>Average Non- malarial months</i>	<i>Average Months WITH Daraprim</i>	<i>Malaria! Months WITHOUT Daraprim</i>
	1493	1490	1823	1415	928	799	764	730				
January	13	28 _a	24	8	14	12	21	31	151	18.9	—	—
February	12	14	13	10	22	19	13	18	121	15.1	—	—
March	14	20	14	7	14	8	13	27	117	14.6	—	—
April	22	29	16	10	13	16	17	31	154	19.2	—	—
May	18	16	30	12	16	20	24	27	163	20.4	—	—
June	12	18	21	4	12	18	23	23	131	16.3	—	—
July	26	20	27	10	21	12	26	31	173	—	19.7	22.8
August	25	51	42	22	10	20	29	40	239	—	19.7	36.0
September	26	54	32	18	14	29 _a	16	57	246	—	19.7	37.4
October	31 _a	46	30	35	20	19 _a	31 _b	40	252	—	23.0	36.4
November	33 _a	39	17	14	16	26	24 _b	15	184	23.0	—	—
December	24 _a	21	9	16	26 _c	18	19	19	152	19.0	—	—
TOTAL REACTIONS									2,083			

NOTES:—

(a) Months in which there was “epidemic” chickenpox.

(b) Months in which there was “epidemic” measles.

(c) Smallpox vaccination with vaccinia.

Average Non-Malarial Months—18.3.

Average Malarial Months with Daraprim—20.6.

Average Malarial Months without Daraprim—33.1.

Thus we have shown that during those months when malarial transmission is minimal there was an average of 18.3 reactions per month; whereas, in the four months when malaria is prevalent and we did not administer pyrimethamine, the average number of reactions was 33.1; and during the four months during the three years when pyrimethamine was given the average number of reactional states was 20.6. Our clinical impression also was that during 1958 when we did not again give pyrimethamine, in spite of improved methods of treatment, especially the use of cortisone and its derivatives, the severity and persistence of reactions were considerably greater than during the three preceding years when pyrimethamine was used.

Thus we suggest that malarial suppression during the months of highest malarial incidence, using pyrimethamine once weekly in 25 mgm. dosage, is of definite value in reducing the number of reactional states occurring in leprosy patients who have those types of disease prone to develop reactional states.

Summary

1. Intercurrent infections are important factors in the inciting of reactional states in leprosy.
2. The wide endemicity of malaria in the tropics makes it an especially important inciting disease.
3. Malarial suppression with pyrimethamine has proved of significant value in reducing the incidence of reactional states in leprosy.

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LEPROSY IN NEPAL

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In the Editorial of the July 1958 number of *Leprosy Review*, there appeared a report from Dr. P. J. Chandy with "News of Leprosy in Nepal".

It may be of interest to readers to bring this up-to-date in so far as more recent news has been received from workers in Nepal.

Dr. Chandy remained in Nepal till the summer of 1958, having already made good contacts, established clinics, and assessed the size of the problem. Dr. J. C. Pedley then took over the work, continued to see patients at a number of clinics, and began the development of the site that had been granted to the Mission by the Government of Nepal. When Dr. Pedley proceeded on leave in 1960 Dr. Katherine Young, assisted by Miss Andrew, took charge of the medical work; while Mr. Dale Leathead, on loan from the Regions Beyond Missionary Union, took charge of the building operations, which he had been supervising since November 1959.

At the Leprosy Clinic begun by Dr. Chandy at the United Mission to Nepal *Shanta Bhawan Hospital* in 1956 records show that by February 1960, 312 leprosy patients had been registered, of whom 113 were reported by Dr. Pedley to be attending regularly on a weekly or monthly basis; Dr. Young reported that 87 attended on one day, of which number seven were new patients. At *Bhatgaon*, where a leprosy clinic has been established in connection with the medical work of the United Mission to Nepal, 78 patients had been registered by February 1960, of whom 46 were reported by Dr. Pedley to be attending regularly.

Clinical work in the Kathmandu Valley

At *Anandaban*, The Joyous Forest, the site of the new *Mission to Lepers Kathmandu Valley Leprosy Hospital*, 37 patients have been registered, with 11 putting in a regular attendance; since Dr. Young's arrival however a new centre has been opened in the valley at the village of Chapagaon; this saves the patients the extra three mile walk to the leprosarium, and already 20 patients are attending, with new patients appearing at each clinic.

At *Kokhna*, the Government leprosarium in the Kathmandu valley, there are reported to be 800 inmates; but 300 are said not to be suffering from leprosy. Dr. Young has been invited by the Ministry of Health to visit this segregation centre and to advise as to what arrangements can be made for the treatment of the patients, for while shelter and food have been provided, little in the way of effective treatment has been offered; many children already show signs of the disease.

Building Operations at Anandaban

There have inevitably been delays in getting the building programme under way at Anandaban, but in June 1960 under Mr. Leathead's vigorous leadership the following position had been reached. Work was well advanced and was proceeding on (a) Quarters for medical staff, and for a Nepalese construction manager. (b) Workshop, store, garage and generator house. (c) Temporary accommodation for patients to be admitted during June 1960. Further work was in hand on the installation of a "hydram" which involved a considerable engineering feat as a 90-in. (27.43 m.) gully had to be bridged to carry a 9-in. (22.86 cm.) pipe across; on staff quarters for a nurse; and for Nepalese workers; on further temporary accommodation for patients. Plans were under consideration for permanent quarters for patients; for additional staff quarters; and for the building of a hospital for the admission and treatment of those suffering from the more serious complications of the disease.

Gorkha District

Miss Nora Vickers, S.R.N., of the *United Mission to Nepal*, has sent news of the situation in the Gorkha District, five days walk from Kathmandu. The area is approximately 870 sq. miles (about 2,253 km.²) and the population of 124,000 includes people from all the castes of Hinduism, and from the hill tribes such as Gurungs, Magars and Tamang Lamas. During the past two years some 130 leprosy patients have been seen at a general clinic held on a mountain ridge at Amp Pipal. Those attending regularly amount to 55, but the tendency for more regular attendance is increasing. All types of the disease have been recorded, but gross deformities were few. Miss Vickers reports that there was some local resentment when it was realised that patients suffering from "The Great Disease" were being treated at this clinic, but threatened demonstrations were forestalled by visiting one or two gathering places and explaining, with the aid of posters, the nature of the disease, how it is spread, and the great benefits that modern treatment could bring to its victims.

Tansen, W. Nepal

Dr. Marjorie F. Foyle has sent word on the work of the *United Mission to Nepal at Tansen*, Palpa, West Nepal. The area covered is about 30,000 sq. miles (about 77,000 km²). No detailed leprosy survey has been possible, but monthly visits have been paid at the request of the health officials to the Government leprosarium at Malunga, six miles from Tansen; the colony consists of three two-storey brick buildings with mud floors. The storeys are divided into enclosures by mud walls, and in each enclosure there lives, as a rule, one family.

There were, in May 1960, 158 patients in the colony—75 men,

46 women and 37 children. Of these 28% (4 men, 7 women and 34 children) show no sign of the disease. A team of workers from the United Mission Hospital at Tansen has paid monthly visits for the past two years. During April 1960 when Dr. Pedley accompanied the team, a survey of the patients showed 46% were Tuberculoid, and 54% Lepromatous. 62% of all cases suffered from deformity of one kind or another, and 63% had or have had ulcers. It is thought that the disease is widespread throughout the district.

Pokhra District

Dr. Ruth A. Watson writes of the work of the *Nepal Evangelistic Band* at Pokhra, 10 days' walk to the West of Kathmandu. To the North, as far as the Tibetan border, and to the West there are no medical facilities at all. Dr. Watson writes "Our patients come from every direction, but we have as yet been unable to do any detailed surveys of many areas. One survey was done, 3 to 5 days' walk to the North West where we already knew there was a great deal of leprosy. This survey confirmed to us the conditions under which these people were living, many of them in caves by the side of the trade route to Tibet where they beg from passing merchants".

"Green Pastures"

The Nepal Evangelistic Band began medical work in Pokhra in 1952, starting with a general dispensary. Leprosy patients were slow to come forward, but as confidence was established patients began to come, not so much from Pokhra itself, as from the villages in the surrounding hills. Some who came had too far to travel for regular treatment, others had been turned out of their homes, and soon a group of patients was living under a tree in the bazar. Feeling that a place should be secured for them as soon as possible, application was made to the Government, and permission was given to buy a tract of land four miles from the bazar. There was no time to erect permanent buildings, so a temporary shelter was put up and the first patients were admitted in September 1957 to the "Green Pastures" lepro-sarium. Here Miss B. C. Bailey, S.R.N., S.C.M., and Miss W. E. Lodge, S.R.N., S.C.M., live along with a Nepali family and a Nepali nurse to assist them. The father of the Nepali family was an out-patient and while attending for treatment became a Christian; the nurse was found to have developed leprosy while she was taking her training in the general hospital. Dr. Ruth Watson as Medical Superintendent pays weekly visits and operates as occasion demands. To date, April 1960, a total of 46 patients have been admitted (30 men, 16 women) and six have been discharged with "negative" certificates.

Meantime, the general dispensary begun in Pokhra in 1952 has grown to a hospital, to which leprosy patients come as out-patients. 187 men and 50 women have been registered, but attendance is far

from satisfactory—the distances are too great, the paths too rough, and often the rivers too high. “We hope”, writes Dr. Watson, “that later on it will be possible to start subsidiary clinics in strategic centres in each direction, run by ex-patients and supervised by regular visits from a doctor or nursing sister”.

The majority of the leprosy patients are reported to be of the lepromatous type. Eye involvement is not common, but foot ulcers are a great problem because of the rough ground, and the fact that nearly all the people are farmers, with but little opportunity of finding alternative employment.

Doctors, nurses, physiotherapists, occupational therapists are all needed to help meet the increasing demands of this work—in India, in Africa, in Nepal, in Korea, in Hong Kong, and in many other countries.

LEPROSY IN THE NETHERLANDS

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From the beginning of this century until the end of the second world war leprosy has been a rare disease in the Netherlands. Only a few new cases are mentioned every year in the annual reports of the Inspector of Public Health.

After 1945 a large number of people have migrated or been repatriated in the Netherlands from countries where leprosy is endemic. The fact that several cases of leprosy and patients in the incubation period of the disease would be among these people did not cause surprise.

Patients can obtain free treatment at the special dispensary of the Gastmann Wichers Foundation at Rotterdam, officially supported by the Ministries of Health and Social Works. Treatment is also free at University Clinics. If patients prefer they may be treated by private practitioners.

The leprosy specialist of the G. W. Foundation is assisted by a full-time nurse-social-worker. Travel expenses are refunded to the patients. Aid is given in regard to rehabilitation, suitable occupation, housing problems, etc. A sanatorium of 40 beds for leprosy patients is maintained by the G. W. Foundation. The building of this was made possible by a generous loan from the Government. The leprosy specialist, accompanied by the social worker, examines all contacts of leprosy patients at least once a year.

The majority of the patients in the Netherlands have taken advantage of the facilities offered by the Gastmann Wichers Foundation. Since 1950, 264 patients have been registered. If known cases treated elsewhere are added and an estimate is made of unknown cases the total of cases in the Netherlands is between 300 and 350.

Therefore, an analysis of the data of the 264 cases registered at the G. W. Foundation gives a fairly accurate picture of the present leprosy situation in this country.

Of these 264 patients, 48 are from the Netherlands, 157 are Indo-Europeans, 16 descendants from Netherlands and West Indian parents, 4 West Indians, 35 Indonesians, and 4 Chinese. Of these patients, 238 were infected in Indonesia, 22 in the West Indies, and one each in Singapore, Hong Kong and Nyasaland.

The type index in all cases is 45%. The differences in type index in Europeans (42%), Indo-Europeans (47%), and Indonesians (46%) are not significant.

There are 183 male and 81 female patients. However, it is not advisable to draw conclusions from this sex ratio, as more European men than women went to the tropics and also more Ambonese men

than women arrived from Indonesia. The Indo-European group is the most representative one and showed a sex rate of 66%, against 75% in Europeans and 80% in Indonesians.

In the European group 43 of the 48 patients were infected in Indonesia. 16 patients were in the army or navy and four of these went for the first time to the tropics after the war. The occupations of the other patients were: missionary, 6; teacher, 4; official, 4; nurse, 2; police, 2; journalist, 1; builder, 1; engineer, 1; student, 5; housewife, 3; without occupation, 2. Although the possibility that some patients were infected in the Japanese prisoner-of-war camps could not be excluded, the evidence was not conclusive.

The importance of examination of contacts of patients is demonstrated in the following figures.

TABLE I

<i>Number of families</i>	<i>Number of patients per family</i>	<i>Total of patients</i>
18	2	36
8	3	24
2	5	10
28		70

Also in 4 married couples a conjugal infection was found and in three families husband and wife were married after the manifestation of leprosy in both. Thus, 84 patients, or 32% of the cases, were found in 34 families. Almost one third of the cases can be explained by contact within the family, or by a member of the family or by a temporary visitor who infected one or more cases in the family. In the remainder the source of infection is often unknown. It may be true that some patients have been unwilling to volunteer information, but it is certain that in the majority of the cases the patient really does not know the source of infection. In these cases there are two possibilities, either the patient was infected by someone who did not show obvious symptoms of leprosy (early lepromatous cases or diffuse lepromatous leprosy) or that in these susceptible individuals only short, incidental, and superficial contact with *M. leprae* was sufficient for transmission of the disease.

In the Netherlands segregation is not compulsory. Although open cases, living in contact with many children or in unsatisfactory conditions in regard to contact with healthy people, are advised to move temporarily to the leprosarium, several open cases are also treated as out-patients. It is of major importance to evaluate the danger of the existing contact with the healthy community.

The majority of the patients had already noticed first symptoms of leprosy before arrival in the Netherlands. In 75 patients first symptoms of leprosy were noticed after arrival.

TABLE 2
Time of Appearance of First Symptoms after Arrival

<i>Years after arrival</i>	<i>number of patients</i>
1	21
2	19
3	15
4	11
5	1
6	4
7	3
11	1
TOTAL	75

As seen in Table 2 first symptoms of leprosy often appear in the first four years after arrival, but thereafter the incidence decreases considerably. Although the incubation period of leprosy is variable, the majority of patients show first symptoms within five years after contact with the source of infection. We have found no reason to assume infection in the Netherlands in the 67 cases that appeared during the first five years after arrival. In the other eight cases we have to choose between a long incubation period or infection in the Netherlands. About these patients the following:

PAT. NI AND N2; Ambonese, reactional tuberculoid type, arrival 1951, first symptoms 1957. Both patients were living in a settlement for Ambonese people. No cases in the family were found. However, in the settlement two lepromatous cases were found. Contact with these patients was denied. The possibility of infection in the Netherlands cannot be excluded; but a long incubation period is still possible. It is also possible that an early indeterminate macule was not recognised.

PAT. B; European, major tuberculoid type, arrival 1939, first symptoms 1945. No cases in the family and no known contacts in the Netherlands. Patient has served in the army in Indonesia.

PAT. V. S.; Neth. X West Indies; minor tuberculoid type, arrival 1950, first symptoms 1956. His brother is a lepromatous patient who showed first symptoms in 1950. Infection in the Netherlands is quite possible, although the possibility that the patient was infected by the same patient as his brother cannot be excluded.

PAT. H.; Indo-European; tuberculoid type, arrival 1950, first symptoms 1957. However, between 1950 and 1954 the patient visited New Guinea and he has no knowledge about contact with patients. He may have been infected there.

PAT. J.; Neth.; reactional tuberculoid type, arrival 1947, first symptoms 1954. No contact known in the Netherlands.

PAT. L.; Indo-European; lepromatous type, arrival 1935, first symptoms 1952. No contact known in the Netherlands.

PAT. V.; Neth. X West Indies; polyneuritic type, arrival 1922, first symptoms 1935. No contact known in the Netherlands. The given date of first symptoms is probably inaccurate.

In none of these cases is there actual proof that the patients were infected in this country, although the possibility remains that this is

true in a few cases. Furthermore not a single case of leprosy has been found in people who never went to the tropics. It is quite possible that in the near future sporadic cases will appear, but at present there seems to be no reason to change the policy in regard to segregation, as it is very improbable that leprosy will become a health problem in this country. On the contrary, it is to be expected that within a few years the number of new cases will decrease again.

TABLE 3

<i>Year of arrival</i>	<i>before</i> 1946	1946	1947	1948	1949	1950	1951	1952
from Indonesia	5	32	11	10	4	30	45	7
from elsewhere	2		5	2	2	2		3
TOTAL	7	32	16	12	6	32	45	10
<i>Year of arrival</i>	1953	1954	1955	1956	1957	1958	1959	
from Indonesia	4	6	41	17	4	18	1	
from elsewhere	2		2	1	4	1		
TOTAL	6	6	43	18	8	19	1	

Table 3 shows that in a period of 14 years 24 patients have arrived from areas outside Indonesia. There is no reason to expect great changes in the numbers of people arriving from these areas in the near future. An average of 2-3 patients per year is to be expected from these countries.

The numbers of patients coming from Indonesia have been very variable. High numbers are seen in 1946, just after the war, when many people left for a leave, or left definitely when Indonesia attained independence in 1950/51 when a large group of Ambonese people was moved to Holland; in 1955/56 when the interior situation in Indonesia became difficult for many European and Indo-European people, and in 1958 when anti-Netherlands activities were followed by another exodus. Compared with the number of people who have moved so far to this country, the number yet to be expected is considerably smaller. Earlier in this article it was shown that the majority of new cases appear within five years of arrival. It is to be expected that the number of new cases from the 1955/56 immigrants will decrease after 1960/61. However, this group is considerably smaller than the former ones. Thereafter a definite decrease in the number of new cases is to be expected.

The importance of New Guinea as a source of infection is difficult to evaluate. The leprosy index along the coast amounts to about 10 per thousand. However, the prevalence is lower in the main settlements where the majority of Europeans live. On the other

hand, there is some increase in the number of Europeans moving to New Guinea and also in the number of Papuans moving from rural areas to the larger towns. As the total number of Europeans in New Guinea is not very high and the leprosy control service is making progress, there is no reason to expect a great number of infections.

A point of interest in regard to the spread of leprosy in the Netherlands is the decrease in the number of tuberculin positive individuals due to the decrease of tuberculosis. Chaussinand¹ has supported the hypothesis that leprosy and tuberculosis are antagonistic diseases. Leiker² has found evidence that in New Guinea the introduction of leprosy in areas with a low tuberculin index is followed by an outbreak of tuberculoid cases of leprosy and that the leprosy index may rise high in a relatively short time. Theoretically an increase of the number of tuberculoid cases is to be expected in Europe too. In practice no evidence of such an increase has been found so far. Undoubtedly, the spread of tuberculosis is not the only factor in the epidemiology of leprosy. If it is true that a hereditary factor is involved it is reasonable to assume that mediaeval leprosy has reduced the susceptible stock in the community. Certainly there are less children born to lepromatous patients than to healthy parents. Hygienic conditions are better than in most countries where leprosy is still endemic. Skin to skin contact is reduced by wearing clothes. Several of these factors working together are probably sufficient to reduce the chance that bacilli enter the skin of a susceptible individual in the European environment.

As long as there is no evidence that even open cases in the community are a danger to the community it is justified to continue the contemporary liberal policy in regard to segregation.

Summary

Leprosy has been rare in the Netherlands, but since 1950 the known cases reached 264, and the estimated total lies between 300 and 350. Patients receive free treatment at the dispensaries of the Gastmann Wichers Foundation in Rotterdam, and at University Clinics, or by private doctors if they prefer, and a 40-bed sanatorium of the G. W. Foundation is maintained for necessary institutional care. The Foundation also maintains a leprosy specialist and a full-time nurse-social worker. The patients originate in countries overseas, and the European patients were infected overseas. Segregation is not compulsory in the Netherlands. The chance of the infection of indigenous inhabitants is not thought to be serious, and because of various environmental factors and because the entry of immigrants from infecting countries has declined, the outlook is good.

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TREATMENT OF ACUTE LEPROTIC NEURITIS WITH HYALASE AND CORTISONE

by R. H. THANGARAJ, M.B.B.S. and Mrs. SAROJINI THANGARAJ, M.B.B.S.
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A total of 40 cases were treated for acute leprotic neuritis in four groups, each group consisting of 10 patients. The patients were put in the different groups by drawing lots. Only patients who had one or two attacks previously were selected for the study.

Investigations

Clinical and electrical assessments of the affected muscles were carried out every week in all the cases. The electrical assessment was done by R.A.F. type II electrical muscle stimulator. Table No. 1 shows the electrical condition of muscles before the treatment.

TABLE 1
Electrical Response of Muscles

<i>Nerve</i>	<i>Normal</i>	<i>Weak</i>	<i>Poor</i>	<i>Total</i>
Ulnar	23	5	—	28
Lat. popliteal	4	2	—	6
Median	3	—	—	3
Radial	—	1	1	2
Gr. Auricular	—	—	—	1
TOTAL	30	8	1	40

The swollen part of the nerve was measured by means of calipers every fourth or fifth day. The progress record was maintained by the physiotherapist.

GROUP A: 1,000 units of Hyalase dissolved in 1 ml. of 1% Lignocaine was injected intraneurally to this group of patients. The second injection was repeated after 4 days. Only in two cases a third injection was repeated.

GROUP B: 0.5 ml. of cortisone acetate (12½ mgm.) with 1,000 units of Hyalase in 1 ml. of 1% Lignocaine was administered intraneurally to this group. The second injection was repeated after four days.

GROUP C: Only 1 ml. of 1% Lignocaine was administered to this group intraneurally. This group was taken as a control group. A second injection was repeated after four days.

GROUP D: This group was given intravenous pot. antimony tartrate on alternate days with an initial dose of 0.02 g. gradually increasing to 0.05 g. Distilled water was injected subcutaneously over the affected nerve to this group. Groups A, B, and C, were given a placebo replacement of pot. antimony tartrate (sterile 1% glucose solution was used for the purpose). This was to satisfy the psychology of the patient.

TABLE 2

<i>Nerves</i>	A	B	C	D	<i>Total</i>
Ulnar	5	7	8	8	28
Lat. popliteal	3	1	1	1	6
Median	2	—	—	1	3
Radial	—	1	1	—	2
Gr. Auricular	—	1	—	—	1
TOTAL	10	10	10	10	40

In the case of lat. popliteal neuritis the limb was immobilized with the knee in full extension and the foot in dorsiflexion. No immobilization was done in the case of other nerves. Of the 40 cases 38 were lepromatous and two were dimorphous.

Results

TABLE 3
Showing the Progress after the Treatment

<i>Groups</i>	<i>Complete relief</i>	<i>Partial relief</i>	<i>No relief</i>	<i>Muscles Paralysed</i>	<i>Relief after stripping</i>
A	6	2	—	1	1
B	8	1	—	1	—
C	5	1	—	1	3
D	6	2	1	—	1

The best results were obtained with group B. The notable thing in this group was the complete recovery of the radial nerve. The patient was not able to lift his wrist against resistance. The electrical condition of the affected muscles was very poor. In the last case of this group the patient developed foot drop immediately after the injection into the lat. popliteal nerve. This was a case of dimorphous

leprosy and the muscles which were normal before the injection never recovered. In another case of dimorphous leprosy Hyalase was administered with Lignocaine, but without success. The results with potassium antimony tartrate and Hyalase were also good but in the control group as many as three nerves had to undergo nerve stripping.

FOLLOW-UP: As we carried out this trial mainly on our in-patients, 36 patients were available for follow-up studies after eight months. Table 4 will show the electrical condition of muscles and the relapse rate in each group.

TABLE 4

Groups	Relapse	Condition of Muscles			
		Normal	Weak	Paralysed	Not available
A.	2	6	—	2	2
B.	1	*8	—	1	1
C.	2	6	1	3	—
D.	4	7	1	1	1

* This also includes the great auricular nerve.

From the above tables we found that the results from group B were very good. I agree that the results will vary very much if all the cases of leprotic neuritis (virgin cases and those who have had repeated attacks) are put on these drugs. Since we started the series with cortisone acetate two years ago this was continued till the end but the results with Hydrocortisone may be still better.

Discussion

We must mention in full the very interesting comment made by Dow in an article on the late results of decapsulation as long ago as 1936. His comment reads as follows: "In the light of the results which have followed upon operations on thickened nerves, we now feel justified in resorting to surgery only in cases of nerve abscess and only exceptionally in these cases it is necessary to decapsulate the nerve. The best results are generally obtained by exposing the abscess, removing the caseous material and closing without drainage. In all other cases of nerve enlargement the practitioner will be well advised to cling to the less spectacular but in the long run more satisfactory medical forms of treatment, for he will find that nerve decapsulation does not realize the hopes raised and its end results are apt to be anything but satisfactory".

In the Purulia Leprosy Home which has 840 inmates and 6,000 out-patients, we resort to stripping only in the following cases:

1. Patients who do not respond to medical means.

2. Tuberculoid nerve reaction when the function of the nerve is threatened.
3. Gradual deterioration in the electrical condition of the affected muscles in lepromatous leprosy.
4. In some cases of dimorphous leprosy.

From the literature we find that several drugs have been tried both intraneurally and subcutaneously along the nerve with variable success.

In 1936 Cochrane and Paulraj tried injection of 80% alcohol intraneurally in two cases with good results.

In 1938 Gass tried cobra venom parenterally with good results. It is interesting to note that snake venom contains hyaluronidase.

Alexander in 1944 tried injection of 25% magnesium sulphate around the nerve. He observed that the effect of the injection lasted for 2-3 months.

Horan in 1949 reported about the successful results obtained from nerve block with 0.15% pontocaine solution with 1/200,000 epinephrine.

Garret in 1956 used Hyalase intraneurally in few cases with encouraging results. The injections were given once weekly and a course of five injections was used as a standard.

In 1957 Jopling and Cochrane tried Hydrocortisone with procaine intraneurally in few cases and later Jopling reported on a case of foot drop in which he administered intraneural Hyalase and Hydrocortisone in procaine solution. The lat. popliteal nerve completely recovered.

In a paper read at the regional conference of the Mission to Lepers at Purulia in 1958, Thiessen reviewed the different measures in the treatment of acute neuritis.

Hyalase increases the tissue permeability and disperses the oedema. Cortisone is a fibrolytic agent and also reduces the capillary permeability thus reducing the oedema.

According to Brand the nerve during the inflammatory stage should be rested in its stretched position. The tissues of the nerve contract and fibrosis takes place during the resolving stage of inflammation. If immobilization is done in its contracted position it ruptures when stretched causing more damage to the nerve.

It is also interesting to note that Hyalase or the combination of Hyalase and cortisone did not have any effect on dimorphous nerves. In one case it actually did harm.

Though the series is small and confined only to certain types of cases, it is evident from the results obtained that a combination of Hyalase and cortisone in lignocaine solution has a definite beneficial effect in acute neuritis.

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REFLECTIONS ON THE TREATMENT OF LEPROSY IN INDIA

by Padmasri Dr. ISAAC SANTRA,
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The Mahabharata describes the battle between the Pandavas and the Kauravas and this story is in the consciousness of all the people in India. The Pandavas represent the good forces which fight against the Kauravas, the bad forces, and convert the world from evil and bring back to it grace, and happiness, and progress. By the transfer of the idea to leprosy the attack on the human body by the Kauravas in the shape of leprosy bacilli is opposed by the Pandavas, expressed in the forms of faith, obedience, diet, exercise, and patience.

Diet in India has great importance and there is great variation. The Punjab has the best general diet and there the incidence of leprosy is lowest in India, and the idea has grown up that countries which have a predominantly rice diet, such as South India, Burma, China, and Japan, have more leprosy. In my childhood the calcium deficiency of rice was compensated for by mixing in black gram which contains twice as much calcium as wheat. Jagannath teaches many things about diet including the utilisation of the red coating of rice and the value of the addition of leafy vegetables. The medicinal value of green vegetables is well recognised in India. With Brahmins it is a rule to take green vegetables every day. Also in India the value of products from the cow is understood. Much dietary information is contained in the customs and writings of the Hindu religion.

I think that the chief factor in the prevention of leprosy is to provide proper well balanced diet to the masses. Exercise is also of great importance and the rich in particular tend to avoid this. I remember the case of a rich woman who improved after I had succeeded in tricking her into getting up and going to the temple every day walking five miles. Also in leprosy treatment of today one should try to get the patient to understand the value of patience and persistence. Modern drugs which I have used include hydnocarpus oil, DDS, thiosemicarbazone, INH, and SU 1906. My experiences of these may be summarised as follows:

Iodised ethylesters of hydnocarpus oil 1% are very useful when given intradermally to the macules of leprosy, in high doses, if possible 20 to 30 c.c. Iodised esters 10% are useful if injected at the side of the thickened nerves and at the side of the trophic ulcers, and if applied to ulcers inside the nose. Lepromatous nodules disappear in a few weeks if carbolised ethylesters 10% are injected in the nodules. For out-patients intramuscular injections are given at fortnightly intervals of 1 part DDS mixed with 5 to 10 parts of ethyl

hydnocarpate in doses of up to 10 c.c., which means that the patient gets 2 g. of DDS per injection.

I give DDS with slow induction of dosage from 10 mgm. to 50 mgm. in three months, and 100 to 300 mgm. over the next two or three years. Reaction is caused by over-dosage, shown by pruritis, sleeplessness, crops of new macules, neuritis and fever.

Thiosemicarbazone is available in India as Novozone and I have found it very useful, and it should be given to cases who cannot tolerate DDS. I give 50 mgm. a day and never exceed 100 mgm. a day.

INH is best in conjunction with DDS and the combination promises better in results than DDS alone. The dosage is 50 to 100 mgm. daily.

The diphenylthiourea, Ciba 1906, promises to be a serious rival to DDS as it is very active and has no toxic side effects. I give a dose of 250 mgm. daily.

I have also used streptohydrazone, which is a combination of streptomycin and INH and it is good for reactional use. I also used Camoquin for acute lepra reaction and hyalase for nerve reaction. Reactions were also helped by injections of calcium gluconate and potassium antimony tartrate. Vitamin B₁, vitamin C, and 25% glucose all mixed and given intravenously each alternate day for six occasions has been used. Recently I have used a combined tablet of DDS, thiosemicarbazone, INH, vitamin B₁, and iron sulphate, called Isoniasulfazone.

THE HUTCHINSON DIETETIC HYPOTHESIS
OF FISH EATING AS A CAUSE OF LEPROSY.
A REAPPRAISAL IN THE LIGHT OF THE
INFLUENCE OF PRO-OXIDANT
NUTRITIONAL CONDITIONS.

by MENY BERGEL, M.D.,
*Director of the Leprosy Research Laboratory,
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In 1906 Jonathon Hutchinson published a book which summarised his observations on some diets which favoured the development of human leprosy. In many countries he found a suggestively high incidence of leprosy in peoples who ate large amounts of decomposing fish. He said "the cause of the disease is some ingredient or parasite generated by or introduced into the fish which has either been not cured at all, or cured badly: it is however quite possible that the ingredient present in the fish may be something quite different from the bacillus itself and that it may even be of chemical nature".

The so-called "fish hypothesis" of leprosy, which came into being as the result of the conclusions of Hutchinson, became the basis of an intensive search for the Hansen bacillus in decaying fish. When the results of this search proved to be completely negative, the postulates of Hutchinson gradually lost strength and were finally abandoned altogether and are quoted today only for historical reasons, although it will be noted that this was not entirely logical, since Hutchinson had specifically stated that the factor in fish might be something other than the Hansen bacillus.

Recent experimental studies and interpretations by the author make it seem desirable to reconsider the ideas of Hutchinson. It now appears plausible to explain the well-established correlation between the occurrence of leprosy and the ingestion of diets high in decomposing fish on the following grounds. Decomposing fish contain relatively large quantities of rancid fats and unsaturated fatty acids, which would be expected to induce a prooxidant condition in the tissues of persons ingesting such fish, and it can be shown that a pro-oxidant condition favours the growth of the Hansen bacillus. This is shown as follows:

- (a) The Hansen bacillus can be made to multiply in rats fed a pro-oxidant diet. Three serial intratesticular inoculations of Hansen bacilli were made in rats kept on a pro-oxidant diet (low in Vitamin E and containing 15% linseed oil), during a period of 26 months. Seven months after the last inoculation the testes were found to contain considerable numbers of acid-fast bacilli^{2,3,4} which were tested biologically in two ways.

In the first test these bacilli were seeded on Lowenstein-Jensen media and were found not to develop colonies at various temperatures, up to a period of 120 days. In other words, the bacilli would not grow in an artificial medium designed for acid-fast bacilli⁴ and in this respect resemble Hansen bacilli. In the second test, a lepromin made with testicular tissue from inoculated rats was tested in the usual manner⁵ along with integral and bacillary lepromins made from human lepromas, and the rat tissue lepromin was found to behave in the same way as the lepromin from the human tissues.

These two biological tests showed that the bacilli found in the testes of the inoculated rats were Hansen bacilli. Likewise, a comparative study has been made of the growth of *M. leprae* inoculated intratesticularly in white rats submitted to various pro-oxidant nutritional conditions. With the pro-oxidant diet employed (Vitamin E deficient diet with linseed oil, with rancid linseed oil, with cod liver oil, with or without the addition of silver nitrate in the drinking water and injection of haemolysates) there was a notable growth of *M. leprae* in relation to their growth in control animals fed on ordinary diets⁶.

- (b) It was possible to demonstrate an antioxidant activity *in vivo* of various antileprotic compounds as follows. Rats kept on a pro-oxidant diet (low in Vitamin E and containing 15% cod liver oil) were found to be protected for periods up to five months against the formation of ceroid pigment in the subcutaneous, perigonadal and perirenal fat by the addition to the diet of 0.2% isoniazid, 0.2% diaminodiphenylsulphone, 0.1% 4-acetylaminobenzaldehyde thiosemicarbazone and 0.5% 4-butoxy-4'-dimethylammonothiocarbanilide. Control animals not given these drugs formed ceroid pigment in the above mentioned tissues in large amount^{7,8,9}. These experiments show that these antileprotic drugs have antioxidant activity.
- (c) But compounds known to have high antioxidant activity and not previously used against leprosy were found to exhibit antilepromatous activity. For instance, the administration of large amounts of Vitamin E (600–800 mgm. daily) to a group of lepromatous leprosy cases was found to exert a very remarkable antilepromatous effect¹⁰. From the experimental findings presented above, it is concluded that there is a very clear relationship between the pro-oxidant state, which favours the autoxidation of lipids, and the pathogenesis of leprosy¹¹. The pro-oxidant state with the accompanying autoxidation of lipids can be produced by the ingestion of decomposing fish. This thus appears to lend support to the "fish hypothesis" as

it was originally postulated by Hutchinson, and moreover indicates the nature of the material in the decaying fish which favours the development of leprosy.

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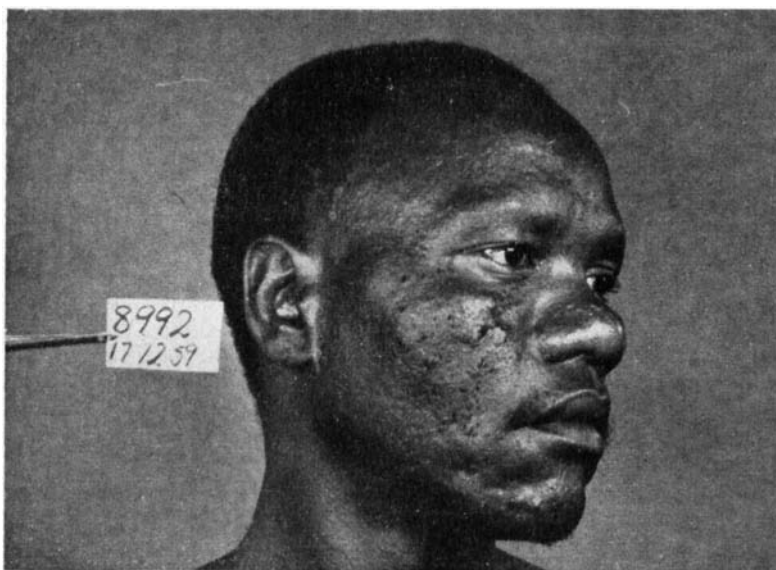
THE TECHNIQUE OF STAINING LEPROSY BACILLI IN SMEARS.

by A. R. DAVISON, M.R.C.S (Eng.), L.R.C.P. (Lond.)

Westfort Institution, Pretoria, South Africa.

In the *Leprosy Review*¹ R. Rhodes-Jones described his modified technique for staining leprosy bacilli in smears. I noted he did not use alcohol in his decolorizer and used toluidin blue as a counterstain. I have previously² drawn attention to the danger of inadequate decolorization when using acid alone for a short period. We have now come to the conclusion that acid alone is an inadequate decolorizer and our present technique is to use 3% HCl in S.V.R. for 15 minutes.

We have occasionally found partially acid-fast diphtheroids in cases of chronic acne. So from patient No. 8992 (Plate I) we took 12



skin smears. The slides were numbered from 1 to 12. The first six slides were stained in the usual manner but slides 1, 2 and 4 were purposely under-decolorized. The first three were decolorized by 3% HCl in S.V.R. and the other three by 5% sulphuric acid. They were counterstained with a saturated watery solution of methylene blue for 60 seconds and the excess stain was washed off with water. Our results are tabulated in Table I.

From the table it will be seen that acid-fast bacilli were found in all slides decolorized by 5% sulphuric acid and where decolorization was incomplete with 3% HCl in S.V.R.

TABLE 1

<i>Decolorizer</i> 3% HCl in SVR.	<i>Time of</i> <i>Decolorization</i>	<i>Results</i>
Slide No. 1	1 minute	3+
2	5 "	2+
3.	15 "	Negative
<i>5% Sulphuric Acid</i>		
Slide No. 4	1 "	3+
5.	5 "	1+
6.	15 "	2+

The stained and unstained slides were then posted to Mr. Rhodes-Jones for his comments. In a personal communication he reported that he first found slide 3 to be 1 plus, but on restaining and decolorizing and using methylene blue as a counterstain he obtained the results in Table 2.

TABLE 2

<i>Slide No.</i>	<i>Method</i>	<i>Result</i>
1	1 min. 3% HCl in SVR.	No AFB in 100 fields.
2	5 min. 3% HCl in SVR.	No AFB in 100 fields.
3	15 min. 3% HDI in SVR.	No AFB in 100 fields.
4	1 min. 5% Sulphuric acid.	30 AFB in 100 fields.
5	5 min. 5% Sulphuric acid.	5 AFB in 100 fields.
6	15 min. 5% Sulphuric acid.	66 AFB in 100 fields.

He then took the unstained slides, stained them in the usual manner, used both methods of decolorization, but used 0.1% toluidin blue as a counterstain. He obtained the results detailed in Table 3.

TABLE 3

<i>Slide No.</i>	<i>Method</i>	<i>Result</i>
7	1 min. 5% Sulphuric acid.	2 bacilli per 100 fields.
8	5 min. 5% Sulphuric acid.	Neg. bacilli per 100 fields.
9	15 min. 5% Sulphuric acid.	Neg. bacilli per 100 fields.
10	1 min. 3% HCl in SVR.	3 bacilli per 100 fields.
11	5 min. 3% HCl in SVR.	Neg. bacilli per 100 fields.
12	12 min. 3% HCl in SVR.	Neg. bacilli per 100 fields.

In his communication to me he makes the interesting statement that "It would therefore seem by my results that if we are counterstaining by either toluidin blue or methylene blue, the diptheroids are effectively masked".

In my view counterstaining is done to make a background to the smear and not to disguise what is on the smear.

I think these experiments justify our contention that alcohol should be used in the decolorizer.

Our present technique is:—

1. Fix smear over heat, avoid charring.
2. Cover the slide with carbol fuchsin solution. The standard is 1 part of a 10% solution of basic fuchsin in 90% alcohol with 9 parts of 5% solution of carbolic acid crystals in distilled water. Heat until it steams for 10 minutes and wash with water.
3. Decolorize in 3% HCl in 95% alcohol for 15 minutes. Wash with water.
4. Counterstain with a saturated watery solution of methylene blue for 60 seconds.
5. Wash excess stain off with water. Allow to dry.

Acknowledgement

I have to thank the Secretary for Health, Pretoria, for authority to submit these notes for publication.

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LETTERS TO THE EDITOR

INSTITUT PASTEUR, PARIS XV

Dear Sir,

Permit me to make some remarks about the article of Professor H. C. de Souza-Araujo "Bacteriology of Rat Leprosy" which appeared in the July number of your esteemed journal (31, 3, 178).

The acid-alcohol-fast bacilli which this author has cultivated certainly do not live in symbiosis with the strain of Stefansky bacilli obtained by the passage on rats of our laboratory. In fact, the lesions of the rats which we send to the investigators who ask for them are always excised aseptically and very carefully controlled from the bacteriological point of view, in inoculating them on various media for culture. Thus all possibility of contamination of our strain by other acid-alcohol-fast bacilli can be excluded. Besides, the very numerous attempts at culture of the Stefansky bacillus which we carry out regularly from the lesions of rats inoculated with this strain have never up to now resulted in the appearance of a culture of acid-alcohol-fast bacilli of any type.

Moreover, at the Fifth International Congress of Microbiology at Rio de Janeiro, 1950, which I attended, Prof. de Souza-Araujo had not envisaged, at any time, the possibility of a bacillary symbiosis, but on the contrary he affirmed that the cultures of the bacilli of Hansen and of Stefansky had succeeded. In the course of the discussion I said that I was persuaded that he was only dealing with para-tuberculous bacilli. I have not changed my mind since then.

If the acid-alcohol-fast bacilli cultivated by Prof. de Souza-Araujo really provide an example of a bacillary symbiosis, and I rather doubt this, this finding is peculiar to his laboratory.

Dr. R. CHAUSSINAND,

THE EDITOR.

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Dear Sir,

I invite your kind attention to the following facts: recently "A Preliminary Report on the Effect of Diamino-Diphenyl Sulphone on Malaria in Northern Nigeria", H. M. Archibald and C. M. Ross, has been published in *Leprosy Review*, Apr. 1960, p. 134, about the efficacy of DDS in malaria. In this connection I have to inform you that I also pointed out the efficacy of DDS in the control of malaria and its suppression. I mentioned this fact in one of my publications under the title "Common Toxic Manifestations with Sulphone in

Course of Mass Therapy, with Broad Management of the Important Ailments", which was published in the Patna Journal of Medicine, December 1958. This fact about DDS and its relationship to malaria was pointed out under the caption "Comment" in the end of the foregoing article, on observations made by me on several patients.

Dr. P.N. JHA
Medical Officer in Charge

ABSTRACTS

Premonitory Symptoms in Leprosy. S. K. CHAUDURI, S. C. BASU, and D. K. CHAKRABORTY. *Leprosy in India*, **31**, 3; July, 1959, pp. 85-89.

The authors describe as promonitory manifestations of leprosy which are helpful in early diagnosis the following: pain, burning sensation, and weakness in the limbs, progressive loss of weight, anorexia and anaemia, spontaneous sores on the limbs, eczema of long duration, and epistaxis. Some of these are only unrecognized signs of established leprosy, e.g. epistaxis. Some of them may belong to other conditions, but the authors think that early leprosy serves as a cause of some of them.

Genetic Control of Isoniazid Metabolism in Man. D. A. PRICE-EVANS, K. A. MANLEY and V. A. MCKUSICK; *Brit. Med. J.*, Aug. 13th, 1960, pp. 485-491.

(The authors deal with a drug of more general use in tuberculosis than in leprosy, but it is used in leprosy, and the principle of genetic control of drug metabolism will be of great interest to all concerned with therapy.—EDITOR.)

In 484 patients the authors ascertained the concentrations of INH in the plasma at six hours from the ingestion of the drug, and found a bimodal curve of frequency distribution. There are rapid and slow inactivators of INH, no influence of sex or age, nor influence of race in the cases treated (American negroes and whites). The slow-inactivating character appears to be recessive. A "dosage" effect of the allele controlling the dominant character is demonstrable in that there is a significant difference between the mean plasma isoniazid concentration of recognizable heterozygotes and the mean value of all other rapid inactivators. The authors make some speculations concerning the factors responsible for the presence and maintenance in populations of the two INH inactivator phenotypes. The metabolism of INH *per se* is unlikely to have been much of a factor in the past, though it could become significant in the future. It is possible that there are naturally occurring compounds which are metabolised in the same way as INH, and that these may possess anti-tuberculous activity. The influence of such a class of compounds might be a mechanism whereby the recessive character might be preserved in populations. Possible advantages of the dominant character are unknown. Harris (1958) found that there is a much higher incidence of rapid inactivators among the Japanese than in European populations. One may presume that the dominant character is more advantageous in the Asiatic environment.

Therapeutic implications of the polymorphism of human INH metabolism are important in three aspects: (1) the development of

polyneuritis with long-term therapy with INH; (2) the response of tuberculous disease to INH therapy; (3) the development of INH-resistant tubercle bacilli. It would seem from the authors' experiments that the trend is for patients with the higher serum INH concentrations to have a quicker reversal to infectiousness than those with lower serum concentrations. The frequency of reversal also tended to be much higher in the slow inactivator group (high serum INH concentration). There seems to be no association between the INH inactivator phenotype and the development of tubercle bacilli resistant to the drug. Further work will go on to try to establish whether the INH inactivator phenotype has an influence on the outcome of the patient's tuberculosis when the disease is treated solely with this drug.

Associação de Estreptomicina e de DDS no Tratamento da Lepra Murina (Association of Streptomycin and DDS in the Treatment of Murine Leprosy.) A. C. MAURI. Rev. Inst. Med. Trop., Sao Paulo, 2, 1; pp. 5-7.

The author found clear evidence that the administration of DDS and streptomycin together to rats inoculated with *M. lepraemurium* resulted in a more pronounced and more rapid regression of lesions than when DDS was used alone. The evaluation depended on a comparison of the size of lesions and their histological picture, and the average duration of the life of the animals. There seems to be a synergistic action between these drugs in murine leprosy.

Tratamento das Amiotrofias Leproticas pela Vitamina E (Treatment of Muscle Wasting in Leprosy with Vitamin E). Priliminary Note. V. M. SARMENTO. Rev. Brasil. de Leprologia, 27, 2, Apr., Jun., 1959, pp. 103-107.

Following O. Sigall, the author in 1956 selected eight cases of wasting of the thenar, hypothenar, and interosseous muscles for treatment by local application of an oily solution of DL alphatocopherol. The results were encouraging but the trial could not be continued at that time. A year later the trial was resumed, using this time also a water-soluble form of acetate of DL alphatocopherol (Ephynal) of which local application of 100 mg. was made weekly for 16 weeks, reaching a total of 1,600 mg. in each region of atrophy. Following Sigall, the needle was introduced into the muscular mass in an oblique direction and obliquely, the needle being drawn back gradually so as to spread the injected substance better. The author reports on one case. The results were very good. After the fourth application the patient began to feel the injections and the thenar and hypothenar eminences began to fill out and flexion and extension improved. This was in the right hand. Treatment was then begun in the left hand, with surprising results, for the hand seemed to return

to normal after the twelfth injection. Photographs are given to demonstrate the improvements.

Effect of Roentgen Rays on Leprous Nodules of Lepromatous Cases.

N. MUKERJEE, S. P. BASU, N. R. SEN and S. KUNDU; *Leprosy in India*, 31, 3; July 1959, pp. 81-84.

The authors discuss this question and describe their own experiments. They find little evidence of effect in doses sublethal to tissue cells. When the X-rays are lethal to bacteria they are lethal to tissue cells. They propose to follow up their 12 cases for any possible late improvement. The dose they gave was 68r per area for two days a week for six weeks.

Treatment of Lepra Reaction with Chloroquine. C. K. JOB. *Journ of Christian Med. Assoc. of India*, 35, 3; May 1960, pp. 184-190.

In the Leprosy Research Sanatorium, Karagiri, the author selected 96 cases of lepra reaction, 81 acute and 15 chronic, and treated them with chloroquine and found it very effective in dosage of 150 mgm. thrice daily for one week, followed by 150 mgm. twice daily for the second week, and 150 mgm. daily thereafter. No serious toxic symptoms were noted, even in some cases who had continuous treatment for 12 months.

Some Recent Chemotherapeutic Work in Leprosy. T. F. DAVEY. *Transact. Royal Soc. of Trop. Med. & Hygiene*, 54, 3; May 1960, pp. 199-206, with discussion pp. 207-211.

The author gives eight illustrations in colour and four black and white of the accompanying histology of cases given Etisul therapy, combined with DDS or DPT (Ciba 1906). He first described the general usefulness of DDS and the sulphones, which have made mass campaigns possible, and there are signs that the sulphones may have a prophylactic value. The need for alternative drugs still remains, to shorten the long periods of treatment and to solve the problems of hypersensitivity to the sulphones, and intolerance to them, and persistent reactive phases, and sometimes failure to respond to sulphone therapy. In the search for such drugs workers owe a great debt to their colleagues in tuberculosis, for new antileprosy drugs seem to come from that field. Controlled therapeutic trials in leprosy face many problems arising out of the lack of knowledge of the bacteriology, immunology, and precise classification in leprosy, and in difficulties about the selection of patients in small groups. In practice the author relies on bacterial indices in smears taken from the skin, takes note also of changes in bacterial morphology under treatment, and uses as a control the curve of bacterial indices worked out over several years for sulphone therapy.

The author described his findings in trials of Ciba 1906 and Etisul. He made trial of Ciba 1906 at the suggestion of Dr. F.

Hawking. He found it as effective as DDS, and more rapid in the first year, non-toxic, so a full dose of 2 g. daily could be given from the start. It did not seem to cause so many reactions, and it combines well with DDS, and he considers it a valuable drug. The work of Davies and Driver led to the choice of Etisul (diethyldithiolisophthalate) as the most powerful of this group against animal tuberculosis. In human leprosy Davey used it by inunction twice weekly in a dose of 6 cc. of the cream. He found it in many cases to have a rapid effect on reducing the bacterial count in six to eight weeks, but an apparent drug resistance is liable to develop in the third or fourth month. He combined it with DDS and Ciba 1906 and found that drug resistance did not occur and the total effect was satisfactory. Etisul seemed to have little action once the bacilli became granular, and erratic results reported by others may be explained by this. He recommends its use in cases with active bacilli, and that its use be preceded and accompanied by DDS and Ciba 1906, or both.

In the discussion following this paper Dr. R. J. W. Rees pointed out the importance and significance of Dr. Davey's work and that carefully controlled clinical trials are not impossible, and confirmed that granularity of bacilli goes with degeneration, as shown by his recent studies with the electronmicroscope. Dr. G. W. Driver gave an account of the laboratory background to Etisul. Its activity is due to the release of ethyl mercaptan in the body. Oral dosing gives rise to ethyl mercaptan in the gastro-intestinal tract and some of this escapes and gives rise to an unpleasant garlic smell. It is absorbed by inunction but the action is systemic. Dr. W. H. Jopling raised the question of the clinical problem of finding a successful and reliable therapy for nerve pains in leprosy and mentioned his clinical trials for leprosy with Vadrine, which in combination with DDS is giving significant results. Dr. D. S. Ridley said that bacteriological analysis of skin biopsies supports the results of Dr. Davey with the new drugs he has tried. Dr. K. R. Chatterjee discussed the possibility of there being different strains of *M. leprae*: he himself thinks this is possible. The granular form may be a stage in development (Manalang) or there may even be a form which is not acid-fast. He found Ciba 1906 effective, and its advantages are low toxicity and effectiveness in some sulphone refractory cases. He found Etisul active when combined with oral DDS and particularly so in patients with no previous treatment.

The Action of Electronegative Colloidal Particles on the Inflammatory Reaction Induced by M. leprae and M. lepraemurium in Rats, Guinea Pigs, and Rabbits. W. A. HADLER, Revista Brasileira de Leprologia, **37**, 1, Jan.-Mar., 1959, pp. 9-14.

Rats, guinea pigs and rabbits were studied histologically in the lesions caused by the inoculation of suspensions of *M. leprae* or

M. lepraemurium together with colloidal suspensions of Prussian Blue, Trypan Blue, or Charcoal. The injections were given by intraperitoneal or intracutaneous routes. In the rat the late lesions produced by the combined inoculation were stronger and more localized and contained larger numbers of macrophages than the lesions due to purely mycobacterial inoculations in the control animals. In limited areas of the lesion the macrophages phagocytise the bacilli and athrocytise the injected particles, and there is some sign of lysis of bacteria and digestion of the electronegative particles by the macrophages. The macrophages in these areas after lysing the bacilli transform into epithelioid cells and the structure of the lesion itself is modified, so that tuberculoid-similar areas develop within lepromatous lesions, though the total histological picture is not modified. The bacilli and particles acting together seem to give an enhanced stimulus, by activating the lytic enzyme system of the rat macrophage.

Correlação e Antagonismo Lepra-Tuberculose: Alguns Aspectos Estatísticos Observados no Estado do Rio Grande do Sul (Correlation and Antagonism between Leprosy and Tuberculosis: Some Statistical Features Noted in the State of Rio Grande do Sul) E. C. DE CAMPOS. Rev. Brasil. de Leprologia, 37, 3, Jul. Sept. 1959, pp. 117–128.

The author quotes the ideas of the various authors for and against the theory of antagonism between leprosy and tuberculosis. He gives data and maps regarding the State of Rio Grande do Sul and compares the coefficients of morbidity for the two diseases which indicate a definite antagonism between them. There is a clear-cut and natural division between the north and south of the State in the matter of the favourable influence of tuberculosis on the leprosy endemic. He thinks there is a practical possibility of stimulating the human body to develop a state of resistance to leprosy, and asks for further investigations in order to reach a definite decision on BCG and other possible agents.

Influencia da Vacinação pelo BCG sobre a Lepromino-Reação em Pessoas Sadias Comunicantes e não Comunicantes de Casos de Lepra (Influence of BCG Vaccination on the Lepromin Reaction in Healthy Contacts and Non-contacts of Leprosy Cases). CANDIDO SILVA and A. RABELLO NETO. Rev. Brasil. de Leprologia, 27, 3; Jul.–Sept. 1959, pp. 129–143.

Since 1952 the National Leprosy Service has been carrying out a trial of BCG in contacts of leprosy cases in the area of the Nova Iguaçu Dispensary in the State of Rio, Brazil, an area where there is close control. All the lepromin-negative contacts were divided into two groups by lot, one group to be vaccinated and the other kept as a

control. The first was given six fortnightly consecutive oral doses of 200 mgm. of BCG. The other group took a placebo of similar appearance. The BCG was in every case used within six days of its manufacture. A second lepromin test was done six to eight months after the BCG administration. A comparative study of the two groups showed practically the same degree of conversion of the lepromin reaction to positive. Subsequent lepromin tests were carried out at variable periods. The authors noted with surprise that some subjects showed reactional instability, turning back to a negative after having reacted very well.

Another investigation was carried out in contacts and non-contacts of leprosy, and did not show any difference between the percentage of lepromin-negatives in these two groups. It was also noted that there was a persistence of lepromin-negatives among contacts of tuberculosis, even in adults.

The authors describe a serious case of a female adolescent who was persistently lepromin-negative, though between 1953 and 1955 she took 2,000 mgm. by mouth. In 1958 she became lepromatous.

The persistence of lepromin-negatives among the vaccinated and non-vaccinated alike, in about the same proportion, severely restricts the preventive value of BCG in the leprosy endemic, for the common opinion is that BCG is only useful in the group which does not react to lepromin.

Metabolism of Compounds Related to Ethyl Mercaptan. J. S. LOWE, Biochem. Pharmac. 3, 1960, pp. 163-172.

Of the striking *in vivo* antitubercular action of ethyl mercaptan and related compounds, also the antileprosy action of an ethyl mercaptan derivative (Etisul or diethyldithiolisophthalate) there are interesting aspects (a) the activity is confined to the ethyl mercaptan series and is not shown by homologous thiols; (b) the antitubercular action *in vitro* is small and no greater than that of other homologous thiols, which suggests that this action is not due to ethyl mercaptan *per se* but to some metabolite.

Snow (Biochem. Pharmac. 65, 1957, pp. 77-82) studied ethyl mercaptan derivatives labelled with S-³⁵ and found that about a half of the S-³⁵ appeared in the urine as sulphate and he detected two organic metabolites, one of which was ethyl methyl sulphone and the other not identified. However, neither showed any antitubercular activity when tested *in vivo*. The present author has studied the fate of the carbon of ethyl mercaptan and describes his experiments, which had results in close agreement with those of Snow. There is no evidence of any direct metabolite from the carbon moiety differing from those in which the C=S link is intact, A possible metabolic path for ethyl mercaptan is removal of hydrogen sulphide by desulphydrase action leaving a two-carbon residue. Subsequent

oxidation of the hydrogen sulphide and metabolism of the two-carbon unit would account for the equivalent production of CO_2 and SO_4^{2-} . Desulphydrases seem to occur generally among higher animals.

Comentarios e Sugestões de uma Campanha Antileprotica Baseados em Nossa Experiencia de 21 Anos no Dispensario de Uruguaiana (Comments and Suggestions for an Antileprosy Campaign Based on 21 Years Experience of the Uruguayan Dispensary) D. DE MENEZES, Rev. Brasil. de Leprologia, **27**, 3, Jul.-Sept. 1959, pp. 144-153.

He studied 101 cases recorded 1939-1959, and found that 56 came of their own accord, seven were sent for clearing up a dermatological diagnosis, six were notified by the Porto Alegre Leprosy Dispensary, nine were on general notifications, and 26 were discovered during examination of contacts. Thus in over 67% of the patients the origin of their infection could not be decided. The author thinks that BCG should be given to the general population, both contacts and non-contacts. Hardly three per thousand of those given BCG developed leprosy in the region.

REPORT

Leprosy News from Formosa. A Review of the Annual Report of the Taiwan Leprosy Relief Association for 1959. By Dr. N. D.

FRASER, Medical Secretary of the Mission to Lepers, London.

Under the title "Closed and Open Gates", and with a cover illustration by the noted Formosan artist, Mr. Ran In Ting, interpreting the story of "The Rich Man and Lazarus in a Chinese setting", Dr. Hugh Macmillan, president of the Taiwan Leprosy Relief Association, has reviewed the work undertaken by those interested in the problem of leprosy in Taiwan.

Real encouragement has been brought to all members of the association by the coming to the island of two devoted and talented leaders. The first is Dr. Kazuo Saikawa of the Nagashima Aiseien in Japan who is an experienced plastic surgeon. He spent five months, from January to June 1959, visiting the Government Loseng Leprosarium, the Happy Mount Colony and a number of clinics. At the Government Leprosarium he performed plastic and orthopaedic operations to demonstrate what can be done to correct deformities and disabilities. Since his return to Japan Dr. Saikawa has offered his services as a Medical Missionary to Taiwan, and he is being sponsored by the Evangelistic Committee of the Church of Christ in Japan. Dr. Saikawa expects to take up residence along with his wife and family in Tainan early in 1960.

The second is Dr. Myles E. Efteland who, with his wife and family, arrived during the summer from the U.S.A. He has been seconded by his Lutheran Mission to work as Medical Director of the Taiwan Leprosy Relief Association and will help to develop and expand the work that is already being done.

Ma-kung Clinic in the Pescadores Islands. Miss Marjorie Bly, R.N., reports on the opening of the Special Skin Clinic for victims of leprosy in the new Provisional Hospital. This is a significant step towards the integration of leprosy into the general medical programme which might well be noted in other parts of the world. It does not mean however that all fears and superstitious ideas have been forgotten for Miss Bly writes "I still recall with a shudder the story of our grandpa patient of 86 years of age. He was threatened with burial alive because it was feared that he might die a natural death. Such an event would mean that the village people would not be able to cook any food for seven days at least, lest the spirit follow the smoke back to the fire and rice-kettle and remain in the village."

Tainan and Chia-yi Clinics. Miss Ruth Duncan, R.N., reports on the rapid growth of these two clinics; 360 patients have been registered, and in one third of them clinical resolution has taken place; many have greatly improved; and much suffering has been relieved. In addition a Rehabilitation Farm has been established, and the first

cottage for four men completed. Peanut, sesame and cotton crops have been raised and "the venture has thus far been a success".

Kaohsiung Clinic. The Kaohsiung Clinic begun by Dr. Bjorgas has registered 410 patients since it was first opened. The work is being carried on by Dr. Kristoffer Fotland with a team of Formosan assistants during Dr. and Mrs. Bjorgas' leave.

Mackay Memorial Hospital. This clinic was begun by the pioneer of leprosy work in Formosa, the late Dr. Gushue Taylor, more than 30 years ago. Dr. Y. F. Chao is now in charge and has a register of 90 patients. During the past four years nine patients have become clinically and bacteriologically negative; 17 have shown marked improvement; 38 minimal improvement, and seven have shown no progress.

The Happy Mount Colony, established about 30 years ago by Dr. Gushue Taylor, continues to make a distinctive contribution to the work by the giving of exemplary treatment under very good living conditions; the venture has been marked by a rapid turnover of patients. Dr. Dorothy Harris and Miss Leicester presented 14 patients for discharge at a special Christmas service. A similar number was discharged in 1958.

At the *Provincial Loseng Leprosarium*, Dr. T. Y. Chen, the Superintendent, reports at the end of the year a total of 1,016 patients. 88 patients became symptom-free during the year. There were 102 new admissions. During the past five years a total of 171 patients have been discharged and rehabilitated. Occupational therapy is becoming an important feature and includes brickmaking, vegetable and fruit growing, and care of livestock. Educational and recreational activities have received special attention with a view to raising the standards of the institution.

The Holy Hope Church records a congregation of 300 patients and exercises a great influence in the life of the leprosarium.

Scientific studies, and the teaching of medical students.

Dr. Shen-ho Lai is continuing his studies on the transmission of leprosy, and on the distribution of the disease throughout the island. He also directs courses of lectures for medical students.

Rehabilitation. Mr. K. Brunner, of Hwalien, reports on steps taken to secure the rehabilitation of two men and two girls from the Happy Mount Colony. Mr. N. has been put in charge of a chicken farm and agricultural work. Mr. L. is working as gardener. "They are now cured of the disease and are finding their way back into ordinary life" writes Mr. Brunner. "Miss T. and Miss C. supervise embroidery and knitting in the Blind Girls Trade School."

REVIEW

Sbornikh Nauchnikh Rabot Po Leprologii i Dermatologii, No. 14, 1960 (Collected Scientific Papers on Leprology and Dermatology); Rostov on Don Experimental-Clinical Leprosarium of the Ministry of Health of the USSR; Chair of Skin and Venereal Diseases of the Rostov Medical Institute.

This publication is in the Russian language, with added summaries consisting of a few lines in French (only a few of the authors give a Russian summary). Prof. N. A. Torsuev has a paper of 45 pages with 8 maps and many tables on a *Study of Leprosy in Old China*, which means up to 1949, when the Peoples Republic of China was established. This is a valuable systematic study of the subject under the headings of diagnosis and treatment in China, and epidemiology, and the organisation of the leprosy campaign. I. A. Kaurov has an equally valuable paper of 51 pages on *Medicinal Plants used in China in the Treatment of Leprosy*. He gives a detailed description of remedies commonly used, with their botanical name, composition, dosage, and mode of use. There are 24 pages of tables of such medicaments under their Chinese and Latin names. (We would like very much to translate these two papers in full into English in order to make them available in some manner to our readers, but so far have not been able to get the time.—EDITOR). The third paper is by G. Moskalenko, on pp. 132–136, who reports on *Three Cases of Secondary Muscular Atrophy of the Skin in Leprosy Patients*. These cases were lepromatous leprosy in regression, and patches of cicatricial atrophy developed in the sites of former lepromata. Prof. N. M. Pavlov on pp. 137–142 discusses the *Retinal Interstitial Substance in Leprosy Patients*. He thinks that specific leprotic retinal lesions exist in the form of stearine spots or beaded spots in the perineural area or at the periphery of the fundus oculi. As for the interstitial substance of the retina, it becomes denser, and the neuro-epithelial layer shrinks, and a moderate turgescence appears in the nuclear and ganglion layer. V. R. Loguinov and T. V. Smourov on pp. 143–146 have a paper on *The Action of the Sulphones in Combination with Certain Anti-tuberculous Remedies on Tuberculous Lung Lesions in Leprosy Patients*. The anti-tuberculous drugs referred to are TB-1, Phthivazid, and Streptomycin. They find that they combine well with the sulphones and tend to make pulmonary tuberculosis in leprosy patients have a more benign course. N. N. Ivanova on pp. 147–151 has a paper on the *Amount of Ammonia in the Urine in Leprosy Patients*. Over two years she examined 100 leprosy patients and 30 contacts, and found that with lepromatous cases, especially in a state of reaction, the amount of ammonia in the 24 hours varied, being raised or lowered. These variations are probably bound up with changes in the acid-alkaline equilibrium. The decrease in

urinary ammonia is noted especially in lepromatous patients in an advanced stage of the disease, who have bacilliferous lesions and a raised blood sedimentation rate. N. N. Ivanova, pp. 152–160, also reports on a study of *Amino-acids in the Urine of Leprosy Patients*. This was a study of 115 leprosy patients over a period of one year, and of 35 healthy subjects. In lepromatous cases, especially during reaction, there was often seen to be elimination of cystine and amino-acids of the leucine group, more rarely of valine and phenylalanine. In about 50% of the cases the urine contained unknown compounds not found in healthy subjects. In 108 of the 115 patients there was a raised level of amino-acids. The most marked changes in quantity and quality occurred in the reactive stages of leprosy. Clinical improvement is followed by the amount of amino-acids in the urine becoming normal. K. K. Kharabadjadov, pp. 161–167, discusses *Methods of Active Prophylaxis against Leprosy* and describes a trial of BCG vaccination, after the method of De Assis, in 489 inhabitants of two villages in the Rostov on Don region. P. S. Grebennikov, pp. 168–180, discusses *Control Methods in the Area of the D'Abinsk Leprosarium*, and gives details of the case recording and case finding methods. E. V. Leontiev and N. N. Torsueva describe, pp. 181–196, the *Use of Pharmacodynamic Skin Tests*. They subjected a group of patients with various skin diseases, including leprosy, to various pharmacodynamic tests. For these they used an ordinary needle, as well as a triple needle, and found the latter more effective. For diagnostic tests it is better to use both, because the triple needle often causes a light erythema to appear, which the ordinary needle fails to elicit.

(1960)

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