REVIEWS

La Lepro. Official Organ of the Japanese Leprosy Association. Vol. 25, No. 5, Sept. 1956.

Y. Kawaguchi has studied *the correlation of tuberculosis to leprosy*, and reports that vaccination of mice with phenol-killed tubercle bacilli did not elicit a resistance to murine leprosy, but a liquid paraffin vaccine of tubercle or of murine leprosy bacilli did cause in the mice a degree of resistance to murine leprosy. A still higher grade of resistance was obtained in mice by vaccination with living BCG. On the other hand, injection of mice with a liquid paraffin vaccine of killed murine leprosy bacilli had no effect on tuberculous infection.

N. Harada reports on *electron microscopy of ultra-thin sections of M. ulcerans*. The internal structure of this organism is very similar to that of *M. leprae*, *M. leprae murium*, and *M. tuberculosis*. It has two types of bacillary bodies, one of homogeneous solid type, and one with various internal structures, and there are intermediate forms between these. There is an enveloping cell wall to the bacillary body, and inside it are large electron-dense granules, small granules, and electron-transparent vacuolated structures. There are also reticular, tubular, and branching string-like structures. (Illustrated by 26 figures.)

N. Hirano and K. Sushida studied *the chemotherapeutic effect of isonicotinoyl-3-methoxy-4-hydroxybenzal hydrazone in murine leprosy* and report that it acts as a bacteriocidal drug in this disease. Subcutaneous or oral administration had a marked effect in a few months. When discontinued, there was sometimes relapse and retreatment seems to have no effect. They postulate the development of drug-resistance by incomplete treatment. They also showed that daily inoculation of the drug for a week could prevent the onset of the disease in mice inoculated with murine leprosy bacilli.

M. Uchida and E. Shionuma discuss *the relation between acute iridocyclitis and erythema nodosum in leprosy patients*. They think they have a close relation, and their seasonal frequency is the same, namely lowest in the winter and greatest in the spring. They also noted in their leprosarium that the two conditions corresponded in general and seasonal frequency both in the chaulmoogra and the sulphone era. They think both conditions have an allergic significance. They were able to examine the histology of 4 eyes which were enucleated from cases which happened to have both acute leprous iridocyclitis and erythema nodosum leprosum: the histo-

logical changes were similar to those observed in erythema nodosum leprosum of the skin.

K. Takeda reports on an investigation of *the spreading reaction of hyaluronidase*. They studied the intracutaneous hyaluronidase spreading reaction in 357 leprosy patients. The reaction is much less in leprosy patients than the normal. It is most marked in the lepromatous type, and is least in childhood and adolescence. The fact that the reaction gradually increases with age is a specific phenomenon in leprosy patients. The height of the erythema nodosum leprosum reaction goes with the lowest intensity of the hyaluronidase reaction.

K. Sugai and K. Fukushi discuss *foamy cells*. The character of the lepra cells or foamy cells of Virchow was previously understood to be due to the action of the leprosy bacilli and their products, but now in the era of efficient antileprotic drugs foamy cells occur in lesions where there are few or no bacilli. By reference to the foamy cells of pneumonia, pulmonary tuberculosis, and lung cancer, it is shown that the presence of a bacterium is not always necessary for the activation of the reticuloendothelial system. Phagocytosis of pathologically isolated lipid was the essential process, and the protoplasm of the cell accumulates fatty substances to form foamy cells. The same thing must be the case in the formation of lepra foamy cells.

International Journal of Leprosy. Vol. 24, No. 3, July-Sept., 1956.

C. B. Lara and J. O. Nolasco of Culion Sanitarium, Philippines, report on further studies of Culion-born children as regards *Self-healing, or Abortive, and Residual Forms of Childhood Leprosy and Their Probable Significance*. Children born of leprosy patients at Culion have been under practically continuous observation over the past 24 years. There were 287 cases who developed lesions of leprosy. The findings are summarized in four tables correlating the course of the disease with the clinical morphology of the initial lesions, the early bacteriology, the Mitsuda reaction, and the histology. About three-fourths of the cases of infection healed spontaneously, and this was apparently permanent. The process of healing seemed to be best and surest in those who had initial lesions of papulonodular and other thickening and definitely circumscribed forms. The infiltrated and diffuse lesions went with the lowest proportion of healing, and the wheal-like and raised and flat macular lesions were intermediate. A higher proportion of healed cases was associated also with low bacterial content of the

lesion and a strong Mitsuda reactivity. Histologically, lesions with undifferentiated round-cell or monocyte infiltrates showed earlier healing than those with the tuberculoid structure, except with the papulonodules. Relapses were chiefly noted within less than three years of apparent healing, became rarer after that, and were hardly seen at all after ten years. Relapses occurred more often where the early lesions were of tuberculoid histology, and also where the early lesions were wheal-like and macular. A small number of apparently healed cases showed inconspicuous residual signs, such as enlarged or tender nerve trunks with or without anaesthesia, and micropapules on or near anaesthetic atrophic scars. Most of them are probably benign, but they could reactivate in later life. An investigation of repeated intracutaneous injection of lepromin in a group of children against controls showed some advantage for those who had received the injections before the appearance of leprous lesions, but the evidence so far is inconclusive, and a further study of this matter is proposed.

The authors raise many interesting and valuable points in their discussion, and the whole paper merits close study.

K. Mitsuda, director of the Aisei-en National Leprosarium, Japan, writes on *Primary and Secondary Tuberculoid Leprosy*, with 1 text figure. He advocates the name "secondary tuberculoid" for the appearance of the tuberculoid histological picture in treated and healing lepromatous leprosy. The tissue granuloma of tuberculoid leprosy replaces the former histopathology and is associated with disappearance of the bacilli and the return of a positive lepromin reaction. Also a biopsy of the lepromin reaction nodule shows a histology very similar to that of the ordinary tuberculoid lesion. If thickened sensory nerves are found, the biopsy of such nerve will also reveal tuberculoid structure.

J. Convit of Venezuela gives his fifth report of *Studies of Leprosy in the German Ethnic Group of Colonia Tovar, Venezuela*, dealing with the morbidity rates in BCG-vaccinated and unvaccinated groups during five years. In the first group there were 584 persons and in the control group 522. All lived in close contact with infectious forms of leprosy. Records began in 1950 and full clinical and laboratory observation was maintained. The vaccinated group yielded three cases of leprosy, which were of the tuberculoid type and healed rapidly, whereas the unvaccinated group produced 25 cases, including 9 infectious cases and 6 indeterminate. The morbidity coefficients of 5, 11 and 45.70 respectively indicate strongly that BCG vaccination has a decided preventive action

against leprosy, as also the fact that no infectious form of the disease was found in the vaccinated group.

A. R. Davison of Westfort Institution, Pretoria, contributes an interesting and provocative paper on *Infections in Leprosy Institutions.* He disagrees with the ideas that leprosy is acquired only or mostly in infancy, and that adults do not need to take precautions against infection. He reviews the literature of infections of members of the staff of leprosaria and gives details of South African cases within his knowledge. Two doctors of the Pretoria leprosarium contracted leprosy. One of these actually injected suspensions of nodules into ten members of the Bantu staff, and probably himself, to prove that leprosy could not be transmitted. The other doctor apparently acquired the infection from a chance operation wound, resulting in a tuberculoid lesion in one finger a few months after the prick. Three European overseers and a nurse who had worked in South African leprosaria also developed leprosy, also ten Bantu males who had no family history of the disease, at ages suggesting they were infected when adult. The danger of exposing a child to infection for as little as six weeks is illustrated by an infant with that short contact with a leprous mother, who developed lesions 1 year after removal from its mother. The author advocates the observance of hygienic rules by staff, and that infected individuals should not come into contact with children.

Sister Hilary Ross of Carville reports on a study of *Magnesium Metabolism in Leprosy.* She investigated 177 cases of leprosy, and 27 non-patients as controls, and found that 132 of the leprosy cases had magnesium levels in the serum within the normal range. Low concentrations were found in 27 lepromatous cases and 1 tuberculoid case, and slightly raised levels were seen in 16 lepromatous and 1 tuberculoid. A clinical diagnosis of amyloid nephrosis was associated with 8 of the low level and 6 of the raised level cases. Leprosy *per se* does not appear to affect magnesium metabolism.

R. Chaussinand of the Institut Pasteur, Paris, discusses the *Standardisation of Lepromin.* He mentions the decline in the ready supply of lepromatous nodules because of the efficacy of the sulphones in treatment, but declares that he himself is less pessimistic than others in this matter. It has led some workers to use high dilutions of the lepromin, and though he thinks many of these are quite effective, he does not approve of the very high dilutions, nor of the addition of reinforcing substances which have no antigenic value. To solve the problem that leprosy workers in

many places are not well equipped, the author has undertaken to prepare a standardized lepromin from sterile nodules that are sent him from overseas. The Mitsuda-Hayashi technique as modified by Wade will be used, and care taken to attain uniformity in the preparation of the different lots for distribution, and the final concentration will be determined by optical density. This product does cause some false reactions, attributable to tissue elements. An attempt was made to secure a more homogeneous suspension of the bacilli by ultrasonic treatment, but it was found that the activity of the product was reduced. From the author's experience with dilutions, he thinks that 1:50 can be used for clinical work and 1:200 for epidemiological studies. The optimal dilution for universal use will be revealed only when dilutions are standardized and studied in various parts of the world.

H. Floch of the Institut Pasteur of Cayenne writes of *The Mitsuda Reaction Using a Phenol Extract of Normal Skin.* Recently Kooij (Internat. J. of Leprosy, **24** (1956), 171-182), and earlier de Faria (Rio de Janeiro, Serviço Nacional de Lepra, 1953) reported Mitsuda-type reactions to a preparation of normal skin. Floch now reports results obtained with a 1:40 suspension of normal skin, comparing it with a 1:750 dilution of lepromin. In 12 lepromatous cases he obtained a few positive early reactions with both antigens. In 145 other leprosy cases, which were indeterminate and tuberculoid, over a half gave early positive reactions to the normal skin suspension, and less than a half gave them to the dilute lepromin. Late reactions occurred in over a half with the normal skin suspension, and in 72% of indeterminate and 90% of the tuberculoid cases with the diluted lepromin.

W. A. Hadler and L. M. Ziti of Brazil report on *Histological Reactions Produced by Experimental Inoculation of M. Leprae Murium into the Golden Hamster*, and include 2 plates with 14 figures. They inoculated intraperitoneally 6 mgm. of *M. leprae murium* into golden hamsters, and this caused a disease which developed slowly and ended with the death of the animal. There was an initial phase of small inconspicuous macroscopic lesions which were histologically of retrogressive nature, and after the 150th day a late phase with larger lesions of a progressive nature. In the early lesions the bacilli are few and show morphological changes, and the lysis of bacilli is probably due to active participation of macrophages. In the late lesions the bacilli multiply actively and do not show lysis. The cells of early lesions have characters between the epithelioid cell of the guinea-pig on the one hand, and the lepra cell of the rat

on the other. The cells of the late lesions have only the characters of the rat lepra cell. The deposition of a " hyalin substance " causes secondary lesions in various organs in the initial phase, and asteroid bodies may be seen in the lesions in the late phase.

Y. T. Chang of Maryland reports further from his studies in the *Chemotherapy of Murine Leprosy*. This is the 5th and deals with the effects of various combinations of DDS, Streptomycin, and INH on mouse leprosy. He found that the suppressive effects of these combinations were definitely superior to those obtained with the individual drugs alone. Arranged in decreasing order of effectiveness the following groups emerged: (1) streptomycin, INH and DDS; (2) INH and DDS; (3) streptomycin and INH; (4) streptomycin and DDS; (5) streptomycin alone; (6) INH; (7) DDS.

In the Editorials, J. M. M. Fernandez discusses *the use of BCG in the prophylaxis of leprosy*, who should be vaccinated, and how and when, and suggests the urgent need of decision on the matter at the next international meetings. H. W. Wade discusses the new and piquant subject of *the cause of damaged ear cartilage in cases of leprosy*. He had submitted this question to many workers and the Correspondence section of the Journal contains varied replies from 21. Dr. Wade analyses these replies. It seems that this " nibbled " or serrated condition of the ear cartilage (a Plate with 10 figures is given as illustration) is rare, and some workers have not seen it. It seems more likely to be associated with lepromatous and borderline leprosy. Most agree that breakdown and ulceration of lesions are involved, and several bring in secondary infections, local disturbance of blood supply, and complicating conditions. It seems worthwhile for all workers to examine their records and to seek to elucidate this condition further. Dr. Wade thinks that it will help our understanding of borderline leprosy.

BOOK REVIEW. **BCG and Vole Vaccination,** by K. Neville Irvine. 2nd Edition 1957, 103 pp., 10 plates in colour, 4 figures. Published by the National Association for the Prevention of Tuberculosis, Tavistock House North, London, W.C.1. (Price 15/-.)

Dr. K. Neville Irvine, adviser in BCG vaccination to the Oxford Regional Hospital Board, has brought up to date this wonderfully concise and clear little book on BCG and Vole Vaccination. Over 200 alterations have been made in the text, and new sections added to deal with the treatment of the normal

vaccination reaction, and of complications. The 8 chapters of the book and the adequate illustrations should leave any worker with a very satisfactory knowledge of the subject. The summary and reference appended to each chapter are of additional value. Every leprosy worker should study this book, because of comparable techniques in his field, and because so much can be learned from these advances in the field of tuberculosis. The use of BCG as a possible preventive inoculation against leprosy makes this book of the highest importance for the leprosy worker.

The Rumanian Medical Review, Jan.-Mar., 1957, the first number of its first year, deserves a warm welcome from all medical workers. It is published in English and contains original and summarized articles on subjects in physiology and pathology, public health, microbiology, parasitology, internal medicine, tuberculosis, neurology, neurosurgery, psychiatry, endocrinology, dermatology, and surgery. It is to be hoped that in such an inclusive Review articles on leprosy will eventually be provided.

La Lepro. Official Organ of the Japanese Leprosy Association. Vol. 26, No. 1, Sept. 1957.

M. Nakamura reports on his studies on *the chemical composition of the murine leprosy bacillus.* The method of trypsin digestion was used to obtain the murine leprosy bacilli from the subcutaneous tissues of rats. Chemical analysis showed a less amount of total nitrogen, carbohydrate, and nucleic acid, and a greater amount of phospholipid and substances extractable by alcohol—ether, than with other cultivable acidfast bacilli.

Y. Takayama studied *the onset of murine leprosy as influenced by previous use of X-rays, cortisone, and other drugs.* It was found that cortisone administration after X-ray irradiation, and cortisone alone, suppress the murine leprosy granuloma to some degree. Toluidin blue or toluidin blue mixed with alum did not accelerate the onset of murine leprosy. Egg yellow or a mixture of ox-serum albumin and ferment extract do accelerate the granuloma to some extent. The same author also studied *intramuscular DDS and Promin intravenously* in murine leprosy and found the latter was superior in effect, and in method of administration and doseage.

K. Ushio, Y. Takayama, and K. Ikeda have studied the effects of 3 drugs in murine leprosy. The first was *isonicotinyl-3-methoxy-4 hydroxybenzal hydrazone.* This had a striking effect both in inhibi-

tion of the disease and treatment. The second was *4:4'-diamino-diphenyl sulphoxide,* and the third was *neo-minophagen AT:* both had small inhibitory effect.

T. Kitagawa and T. Nagata discuss *lower limb amputations* in leprosy. They think that the need for surgical treatment is increasing because of the advance in the chemotherapy of leprosy. They studied 114 patients and found that amputation of both legs had been necessary in 33, and that 71 patients with tuberculoid leprosy had required amputations against 43 lepromatous. The essential cause for most amputations was perforating ulcer of the foot. The site of amputation in most cases was the middle or lower third of the leg. The sequelae were neuralgia and pains on pressure or contusion in half the cases, and ulcer of the amputation stump in half the cases, and there was considerable wasting of muscles and no benefit in this regard from a prosthesis. Fall in temperature in the amputation stump was not invariable, but it did occur in the lepromatous patients, to a 3.7° C. decrease.

International Journal of Leprosy. Vol. 24, No. 4, Oct.-Dec. 1956.

J. Convit, C. Sisiruca, and P. Lapenta of Cabo Blanco Leprosarium, Venezuela, give *Some Observations on Borderline Leprosy.* They point out that the inclusion of the borderline group in classification is a valuable contribution to the understanding of leprosy. They collected 286 cases from their area for study and note that they constituted 3.2% of the known cases of the disease. They closely studied 100 dimorphous cases in hospital, and found that 43 of them had a "facies dimorpha," consisting of a bat-like configuration of the infiltration on the forehead, between the eyebrows, on the bridge of the nose, and on the chin and cheeks. Also they noted hypochromic halos round some lesions in 27 cases, and think it is a process secondary to regression of lesions. Hyperchromic patches, secondary to the regression of infiltrated lesions, were very typical, and found in 61 cases. It is important to distinguish them from those of indeterminate leprosy. The borderline hypochromic patches have the features of possessing a possibility of growth, and will show a borderline histopathology: the nerve disturbances are variable. They can evolve into lepromatous (which is the more frequent) or into tuberculoid (infrequent) or progress centrifugally as hyperchromic patches. Such lesions can exist from the beginning with borderline histology.

In 21 cases the authors tried out daily intravenous injections of methylene blue, and found that the dye was retained where

histologically-proved lepromatous changes existed, and pure borderline lesions did not retain it.

Electrophoresis tests of the plasma of 30 cases showed a normal albumin-globulin ratio in 60% of them, which were in regressive activity. In the rest the ratio was below the normal value, and in this group the lesions were tending to persist and spread.

C. B. Lara, C. A. Palafox, J. L. Ignacio, and J. O. Nolasco, of Culion Sanitarium, Philippines, give their first report on their *study of Children of Leprosy Patients Isolated at Birth, given Lepromin and BCG Injections, then Returned to the Colony.*

In an 8 years study so far, 100 children born at Culion of leprosy parents have been isolated at birth. Later 55 have been returned to their parents in the leprosarium after their Mitsuda reactions have become moderate to strong, and 11 have been released to their families outside the leprosarium: by March 1956 there were 33 remaining in isolation and 1 had died.

Repeated lepromin tests were given to 40 children: by this means 16 did not attain 3+ reactivity and BCG was used for them.

Of the 11 children released to guardians, 5 were lost to observation, and 4 have remained free of leprosy, but 2 who returned to the leprosarium at 3-9/12 and 1-7/12 years of age later developed leprosy after exposure periods of 2-5/12 and 3 years respectively. These periods are similar to the average incubation periods for children unisolated and under constant exposure. Neither of these positive cases of the development of leprosy had received breast feeding: one had attained only 1+ lepromin positivity: the other had not received lepromin, nor BCG. No child developed leprosy while still in isolation, though 51 of them have been isolated for 3 to 6 years. By contrast, in slightly younger unisolated children 46 or 36.2% developed leprosy. Congenital transmission therefore seems of no importance.

Of the 55 children returned to the leprosarium, 46 show no evidence of leprosy after an exposure of 1 to 1½ years: longer observation is needed (3 more years) before it will be possible to assess the protective value of prolonged isolation from birth, and of lepromin and BCG injections. The authors think that much more careful study and evaluation of BCG is needed before it can be given a sure place in prevention of leprosy, and more consideration should be given to the sensitizing action of previously-injected lepromin on young children who are Mitsuda-negative, as they have regularly observed this beneficial effect.

A. R. Davison reports on a *Clinical Evaluation of INH as an Adjuvant in the Treatment of Lepromatous Leprosy*, with a note on the *Detrimental effect of Erythema Nodosum Leprosum Reactions*. The study was carried out on 129 lepromatous patients. Of these, one group of 40 received only sulphones, and served as the control. Another group of 40 received sulphone plus INH. The third group of 39 patients received INH, DHSM (dihydrostreptomycin), and PAS. The fourth group contained 10 patients for a pilot study of streptohydrazid, of which each vial contains 1 gm. of streptomycin and 266 mgm. of INH combined in one molecule. A previous investigation under the auspices of the Leonard Wood Memorial Foundation showed that the sulphones alone, and DHSM and PAS, had been the most efficacious. Therefore in the present investigation INH has been added to these drug plans. The duration of the present study was 2 years. The author found that the previous method of giving numerical values for clinical improvement was not satisfactory, as the degrees of activity of lesions is more important than their mere presence, and he suggests that the bacteriological index is the only reliable standard.

In the present series there was clinical improvement in almost all the forms of lesions in all the four groups under treatment. Taking the infiltrations as being the most typical form of lesion and the most susceptible to clinical change and assessment of the same, it was noted that the degree of improvement was almost identical in all the groups, and the bacterial indices were also very similar in all groups.

The author observes that erythema nodosum leprosum has increased tenfold since the sulphones were introduced, that it is not an allergy to sulphones, and occurs almost exclusively in bacilliferous cases. He found 59 cases with ENL, and found that the reduction in the bacterial index was much less than in the 58 cases who did not have ENL (12% against 42%), and hence this reaction is detrimental to the patient and calls for control, in which corticosteroids should be considered.

D. L. Leiker reports on 2 cases of the *Mononucleosis Syndrome in Leprosy Patients Treated with Sulphones*. The patients, both aged 25 years, were under treatment with DDS for major tuberculoid and atypical lepromatous leprosy respectively. Five weeks after the treatment was begun they showed severe symptoms typical of infectious mononucleosis, with accompanying high white cell count and high percentage of mononuclears. One patient had a short relapse but recovered completely. The other patient died after 10

days with severe liver damage and agranulocytosis, after having a bullous dermatitis which subsided under cortisone. In Nigeria in 1949 Lowe described the occurrence of the mononucleosis syndrome in sulphone-treated leprosy patients, but considered it to be a true infectious mononucleosis precipitated by the sulphone treatment: it has not been mentioned by other workers since then. The condition seems to be limited to the first 2 months of treatment: a true infectious mononucleosis should turn up in later periods of treatment as part of a wider endemia. Further, within 2 months of PAS administration, similar syndromes have been reported. In Netherlands New Guineas not a single case of infectious mononucleosis has been reported in the past. From all this the author thinks that the syndrome is not the true infectious form but is a delayed allergic reaction of the reticuloendothelial system induced by sulphones and other drugs, and prefers to call it " mononucleosis syndrome." Early treatment with antihistamines, cortisone, or ACTH seems indicated.

In an addendum the author reports a third case, æt. 26, in whom the syndrome began about 7 weeks after sulphone treatment had been started. There was also a generalized exfoliative dermatitis. Cortisone treatment was used at once, with speedy relief of all symptoms. The blood picture at onset was, white cell count 9,800 with 66% mononuclears; at 2 weeks after onset, leucocytes 21,500, mononuclears approaching normal, at 5 weeks after onset, leucocytes 8,600 and mononuclears 30%.

C. H. Payne gives a clinical note on a case of *Leprosy and Granuloma Annulare in the Same Patient.* This was a female of 42 years who presented skin lesions of the lower limbs of many years duration. She had spent 3 years in various clinics and received a number of diagnoses, but finally leprosy was recognised. The lesions appeared to be tuberculoid, but all smears were strongly positive for bacilli. After 9 months of sulphone therapy the smears became negative and remained so, but the lesions persisted without change in size. Their appearance changed in the direction of flattening, and the assumption of a bluish tinge, and a biospy specimen suggested granuloma annulare. Under corticosteroid therapy there was considerable improvement. The author enquires if other cases have been experienced of this conjunction of granuloma annulare with leprosy.

Prof. Sabura Sato, of Tokoku University, Sendai, Japan, reports on a case of *Nerve Abscess in Lepromatous Leprosy*, and reviews the reports of *Nerve Abscess in Japan.*

The nerve abscess in the case of lepromatous leprosy occurred in two ulnar cutaneous nerves of a male æt. 18. The abscess swelling contained purulent matter made up chiefly of lepra cells, particularly foamy cells, but few leucocytes, and there were many leprosy bacilli. There were no cultivable bacteria. The histological picture showed a highly infiltrated and thickened nerve sheath, with an increase in the fine fibrils in delicate networks, round cells and lepra cells being contained among the fibrils. The nerve cord as a whole had become a lepromatous granuloma consisting of lepra cells and many large foamy cells. Round cells and polymorph leucocytes were very scanty. There was a widespread destruction of nerve fibres, so that only a few or traces of them remained in the increased fibroblasts and connective tissue fibres. No trace of tuberculoid structure or caseous necrosis was seen, such as strikingly occur in the nerve abscess of tuberculoid cases.

Two other cases of lepromatous nerve abscess recorded in Japan are mentioned which had the same essential features, and the rarity of abscess of the cold type in lepromatous leprosy is reported. Reports of cold abscess in tuberculoid leprosy are given for 13 cases in the Japanese literature. This tuberculoid cold abscess is derived from liquefaction of the caseous nerve lesions, and lepra reaction is one of the main causes of the development of abscess. The caseous neuritis, which is the basis of abscess formation, is common in Japan, whereas the typical nerve abscess is rather rare.

T. F. Davey contributes an analysis of the data of Lowe and McNulty on *Tuberculin and Lepromin Reaction in Nigeria.* Special attention is given to the results of low dose tuberculin tests and later of high dose tests in the negatives. The results are correlated with the lepromin reaction.

Out of 278 healthy adults, 79 or 29% were positive to the low dose von Pirquet test, and 96% of these positives also reacted to lepromin. However a large proportion of the negatives were also negative to lepromin. Of the 199 persons negative to the first tuberculin test, 144 or 73% were positive to the high dose tuberculin. The greater part of these positives (84%) reacted to lepromin, and a half of the negatives were also negative to lepromin.

There was a basic similarity in the results of 81 children who were tested, though with important quantitative differences. Only 10, or 12% of the children reacted to the low dose tuberculin, but as before almost all (90%) were positive to lepromin. Of the 75 negative to the low dose tuberculin a bare majority of 52% reacted

to the high dose tuberculin. Again, of these positives 59% were also positive to lepromin, but all who reacted to the high dose tuberculin were negative to lepromin.

It is clear that in almost all subjects who had high sensitivity to tuberculin there was an associated positivity to lepromin, and the correlation was marked for those who were only positive to high dose tuberculin. There was no such correlation for those who were absolutely negative to tuberculin. It is thought possible, and even probable in the case of children, that some of the reactions to high dose tuberculin were of non-specific nature. A point of great interest which requires deeper study is the specific inability of lepromateous patients to convert into lepromin reactors, though hypersensitive to tuberculin and having been inoculated with BCG.

J. H. Hanks of the Leonard Wood Memorial Laboratory, Harvard, has studied and reports on *Quantitative Aspects of Sampling Leprosy Skin Lesions by the Scraped Incision Method.* The scraped incision method of Wade is simple, convenient, and efficient. Hanks has found that a simple modification of the habitual method of making a film can improve still further the uniformity and senstivity of the bacteriological examination. This modification consists in spreading each sample of material to the greatest limit before drying begins, though not forcing it, so as to allow of a natural spread of the cells which make up the material. If desired, still further sensitivity can be obtained by increasing the thickness of the film up to 4 times that recommended for routine purposes. He found that such films may be 14 times more sensitive than average films, and 56 times more sensitive than the thinnest clinical films. Finally, to examine all tissue fragments and cell clusters in each film is another method of increasing sensitivity.

T. Tanimura, H. Honda, and T. Oshima, of the Department of Dermatology of Osaka University Medical School, in their *Studies in the Serology of Leprosy,* report on the *Complement Fixation Reaction by a Modified Antigen.* The authors review previous work on cephalin among the antigens used for carrying out the leprosy complement fixation test, and go on fully to describe their construction of an antigen which contains cholesterin, cardiolipin, and a mixture of cephalin fractions, with added kaolin, which antigen shows a great deal of specificity for leprous sera. The cephalin fractions are those obtained by Folch's method, namely phosphatidyl-ethanolamine diphospho-inositide, and phosphatidyl-serine. In trials to find out the best proportions of these fractions for use in the cephalin part of the antigen, they found these should be 29:10:1 respectively, of solutions of 1% in ether.

With this mixture of cephalin (1% in ether), Cardiolipin (0.2% in alcohol), and cholesterol (1% in alcohol) in the same way they found that the best proportion of the 3 basic solutions was 10:5:1 respectively.

Tests in 110 leprous sera produced high percentages of positives in the three forms of the disease (the lowest in the tuberculoid, but even then 74%), and the total positives were 87.3%. Negative results came from all the sera from healthy subjects, 19 tuberculous and 6 cancer cases. Three or 7.3% of syphilitic sera were positive, and 2 out of 10 pregnancy cases, or 20% were positive.

Tests repeated after an intervals of 6 months in 4 lepromatous cases who were improving clinically showed no material decrease of positivity of the tests. In so short a time it seems that serological improvement in leprosy should not be looked for. The authors think that the cephalin-cardiolipin-cholesterol antigens are suitable for clinical use, as they possess high antigenicity in all forms of leprosy, but give few group haemolytic reactions with sera of tuberculosis, syphilis, and cancer, and normal persons with the exception of pregnancy. The reaction has been called the Handai method, after Honda.

L. Kátó and B. Gôzsy, of the University of Montreal Institute of Microbiology and Hygiene, have studied the *Action of Histamine and Antihistamine on the Ingestion of Murine Leprosy Bacilli by Macrophages of the Rat and the Guinea-pig.* The antihistamine used was synthetic, mepyramine maleate. The influence of the histamine and the antihistamine was studied on the power of the macrophages of peritoneal exudates of guinea-pigs and albino rats to phagocytize the tubercle bacillus from a culture of BCG and the murine leprosy bacillus from a suspension of leproma. The ingestion of BCG by the cells of both animals was stimulated by the histamine and inhibited by the antihistamine. On the other hand, the phagocytosis of the murine bacillus was not affected by either of the two substances, and this applies to both exudates. A crude aqueous extract, free of bacilli, from the rat leproma, inhibited the phagocytosis of BCG by guinea-pig monocytes. The extract of rat lepromin and the antihistamine cause similar morphological and functional changes in the monocytes, namely deficiency of pseudopodia and vacuoles, contraction of the cell, and passive behaviour with BCG. (5 illustrations.)

G. L. Fite discusses *Leprosy, Society, and Hansen's Disease.* He mentions the great vogue of the use of the term " Hansen's disease " and acknowledges the successful spread of this name for

leprosy. In analysing the cause of this success he traces it mainly to social attitudes. The social forces in leprosy are more powerful than the individuals or agencies involved, and these forces tend, not only to stigmatize leprosy, but also to throw a veil of magic over it instead of getting down to matter-of-fact control of it in the light of what knowledge and resources we have. The physician who is genuinely interested in leprosy is baffled, frustrated, and wearied by the false attitudes to it and the inevitable counter-arguments. He mentions leprophobia as one of these false attitudes and says that even education is not a sure cure for it; nor is it wise to adopt the counter-attitude of condemnation of anyone who has this foible. There is also the negative leprophobe who treats the danger of contagion with contempt, and the infectious leprophobe who spreads his fear on to others. Leprophobia does not exist, except as the occasion for it may arise, but it can then develop with extreme rapidity, for there is always a latent background attitude of hatred or loathing. He points out that in the case of poliomyelitis and cancer publicity campaigns have been run, and have taken advantage of the fear of them already existing in the public mind, with good effect, in that vaccination and early treatment have been "got across." The similar social fear of leprosy can be used to give a similar good result. The campaigns against poliomyelitis and cancer had something solid to offer, and in leprosy we should similarly point to the treatment of leprosy by the sulphones, and not make too much in propaganda of coining new names for leprosy or curing leprophobia. As regards the use of "Hansen's disease" for leprosy, the trend is away from using personal names, and the author thinks that the use of this name will never be more than a temporary expedient. The physician's duty is to apply himself to the immediate problem of leprosy as a chronic infectious disease, without permitting himself to be diverted by the social complexities.

The *Editorial*, by H. W. Wade, on the *Lepromin Reaction and Non-Specific Reactivity to Tuberculin*, provokes deep thought on the relationship between leprosy and tuberculosis and suggests study along the lines of lepromin reactivity correlated with two-dose tuberculin testing. Wade refers to the work of Lowe in Nigeria and Guinto in the Philippines on the relationship between the lepromin and tuberculin reactions, and the emergence from their work of the possibility that high-dose reactions to tuberculin may be non-specific in nature, which idea is also developed by Palmer and coworkers. McFadzean prepared a report on Lowe's subsequent findings in tests of 621 children æt. 5 to 16 years. A high total tuberculin-positive rate was found, with no evidence of a

relation to leprosy infection, yet the prevalence of tuberculosis in the community was low. On the whole, there was a significant correlation between the lepromin and tuberculin reactions, but the correlation was relatively poor among subjects who reacted only to high dose tuberculin. It looks as if the unknown antigenic factor behind the high dose tuberculin positives is not so effective for lepromin reactivity: on the other hand a very large proportion of the few who failed to show even the low-grade sensitivity to tuberculin failed also to react to a single dose of lepromin.

Wade then turns again to the Lowe data, as re-examined by Davey, and compares them with a similar study made by Guinto, Doull, and Mabalay. In adults a very large number of positive lepromin reactions went with only mild degrees of tuberculin sensitivity, and many with none at all, and in children the results strongly indicated the existence of non-specific reactions to tuberculin. As regards the reasons behind the large dose reactions one cannot assume they are necessarily due to infection with the tubercle bacillus, and that they are due to mycobacteria other than the tubercle bacillus does not seem likely. Wade postulates that an individual may be *conditioned* to react by non-specific means. He points out that BCG is a non-specific means of inducing lepromin reactivity, and this reactivity is widely held to be protective, even as the " natural " form of it is supposed to be. He sees no reason why the lepromin positivity associated with non-specific tuberculin sensitivity to high doses should not contribute to resistance to leprosy infection.

There is suggestive further evidence of the existence of non-specific reactivity in the report of the Medical Research Council (U.K.) on tests of 56,7000 schoolchildren with low and high tuberculin doses, though the idea is not discussed in the report.

In the *Correspondence* section Dharmendra and K. R. Chatterjee correct and amplify their previous article on the *Prognostic Value of the Lepromin Test in Contacts* (Internat. J. of Leprosy, **24**, 1956, pp. 315-318). Dr. Huldah Bancroft add a note from the statistical point of view. Dharmendra does not think that the results given in his addendum provide an indication of any protective value on the part of the repeated lepromin tests. Dr. Huldah Bancroft, on the other hand, thinks the evidence is statistically strong enough to suggest that there is.

G. Basombrío of Buenos Aires raises questions of the *significance of lepromin positivity*, referring to a statement by Prof. J. Gay Prieto which mentioned exceptional positive Mitsuda reactions in lepro-

matous cases. Basombrío asks for answers from workers on (1) Has it been proved that the immunity state of children with a positive Mitsuda is of no significance? (2) Are there lepromatous cases which give spontaneous positive Mitsuda reactions? (3) Information from the experience of other leprologists on children with positive Mitsuda who later developed lepromatous leprosy? The Editor adds a comment to remind us about lepromin-reactive lepromatous cases being possibly borderline previously.

J. M. Fernández defends his *choice of the right scapular region of the back for routine testing with lepromin*, giving his opinion that the thicker firmer skin is more suitable for nodular reactions like the Mitsuda, there is more room on the back for multiple testing when required, and the patient cannot see what happens to injections on the back.

D. E. Morton reports such details as are available of a case of *activation of leprosy associated with ACTH and Cortisone Treatment*. The corticosteroids were apparently given to a female æt. 71 in the quiescent stage of lepromatous leprosy and continued for several months. The patient felt that her condition grew steadily worse on these drugs, and the records of her clinical condition support that this was so. There was no check available of bacterial index during the period covered by cortisone therapy.

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This special number contains a *symposium on erythema nodosum leprosum*. Prof. J. Ramos e Silva in his presidential address defined the syndrome and its relations. Dr. L. M. Bechelli in his paper studied the clinical features and differential diagnosis and the frequency of its occurence in leprosy patients, which in his experience is considerable in lepromatous cases. Prof. H. Portugal reported on *histological and laboratory findings*. In 9 cases out of 12 studied, the lesions were similar or equivalent to the granuloma described by Miescher (Acta Derm. Ven., 27: 447, 1947), comprising a histiocytic infiltration in the adipose tissue or collagen. Dr. A. Porto Marques also discusses the histology and laboratory data. Out of 7 cases bacilli were present in 5, and the bacilli showed granulation and changes in shape and size. In parts of the subcutaneous adipose tissue there were many vacuolated cells full of bacilli, and similar cells could be found round the sweat glands. Clumps of bacilli or small globi could be observed in vacuolated cells in the suppurative and necrotic foci. Dr. P. Rath de Souza

dealt with the same subject. In sections he found vascular dilation with interstitial oedema and exudation of neutrophil and sometimes eosinophil polymorphs. This exudate is always in relation to lepromatous infiltrations, and these are regressive, since the cells appear vacuolized from the presence of lipids and show a pyknotic nucleus. Bacilli may be numerous or few or absent, and granular forms predominate. He thinks there is a constant relation between the reactive lesion and the lepromatous lesions, and that the latter show regressive features, and this is confirmed by Wade and others. He thinks there must be always a lepromatous lesion in existence to precede the reactional one. He found no example of the granuloma of Miescher in the biopsies he examined. He defines the leprotic reaction as an intercurrent exudative process implanted on a pre-existing lepromatous granulomatous process. It seems as if in lepromatous lesions in regression, a leucocyte-stimulating substance arises. Whether it is bacillary or cellular in origin is unknown.

Prof. F. E. Rabello took up the *general pathology* of the condition. He points out that the erythema nodosum phenomenon is not confined to leprosy, but can occur in connection with tuberculosis, BCG inoculation, coccidiosis, streptococcal tonsillitis scarlatina, cerebrospinal meningitis, ganglionar lympho-reticulosis, venereal lymphogranuloma, and sarcoidosis. In connection with all these he detects a factor of basic infection as the primary specific stimulus, a homologous or heterologous factor which builds up the state, and a precipitating factor which brings it out and which is almost always some drug which is used. Dr. Nelson Souza Campos discusses the same subject. He points out that erythema nodosum leprosum exclusively occurs in the lepromatous type, in which the leprosy bacillus is living practically as a saphrophyte, with the miniumum of indication of any resistance on the part of the body. In this state an apparently allergic reaction supervenes, and the cause of it is by no means clear. An intercurrent tuberculous infection has been suggested, as tuberculin sensitivity is common in reacting lepromatous cases, and the use of BCG seems to desensitize such cases and improve and attenuate the reactions.

Prof. R. D. Azulay discusses the *immunology* of the condition. It only occurs in the lepromatous form, but many lepromatous cases escape it. Bacteriological and histological findings are discordant, and either specific or non-specific causes can release the reactions: hence erythema nodosum leprosum is the clinical expression of a different way of reacting for some of the lepromatous cases. There is contained in the picture a factor of allergy or para-allergy. Dr.

Candido Silva discusses the same aspect and describes his findings in cases of lepromatous leprosy subject to attacks of leprotic reaction and erythema nodosum who were tested with haemagglutinins and antigens made from the leprosy and other mycrobacteria. Attempts at desensitization were made with polysaccharides of *Pseudomonas aeruginosa*, colon bacillus antigen, and autogenous streptococcal vaccine. The results were not suggestive, though there were indications of some difference between erythma nodosum and ordinary lepromatous cases. The clinical diversity and the rhythm of the evolution of the disease are parallel with the immunological findings.

Dr. J. Baptista Risi studies the *prognosis*. While it is impossible to be dogmatic, he thinks the prognosis tends to the favourable side. The deadly equilibrium and indifference to the bacillus on the part of the body at least is broken and the level of resistance is raised. Non-leprotic forms of erythema nodosum do not aggravate the respective diseases associated with them, and it may be the same with the leprosum form. Furthermore, it is an acute manifestation, not so bad a thing as progressive lepromatization, and it is absent in advanced lepromatous cases. He thinks that haemagglutination studies do reinforce this idea of the harmlessness of the reaction and cites clinical comparative studies where the reactive group made better progress in the long-term view.

Dr. Gilberto Mangeon discusses *treatment*. There is no entirely satisfactory method of removing the reaction and preventing its recurrence, and some workers think it should be stimulated rather than suppressed, because it is beneficial. He thinks each case should be decided on its own merits, after careful clinical study. Treatments which are used to control the syndrome are many, and include (1) Change to injectable sulphone for mild attacks of erythema nodosum leprosum occurring in the course of sulphone therapy. (2) Anti-allergic, desensitizing, and stimulant treatments include (a) daily intravenous injections of 2% calcium chloride up to 20 c.c., (b) injections of 10% sodium hyposulphite and magnesium hyposulphite up to 10 c.c., (c) intravenous 10% calcium gluconate, (d) daily intravenous glucose saline, isotonic, 25, 30, or 40%, (e) the desensitizing and detoxicating action of strontium in form of a series of 10 daily injections intravenously of 0.45 in 5 c.c. of methylglioxilate of diethylenediamine, (f) auto- and heterohaemotherapy in increasing doses, (g) intramuscular or intravenous injections of Vitamin C in daily doses of 50, 100, and 500 mgm., (h) antihistamines such as benadryl, (i) transfusion of whole blood, 250 c.c., has good results which are evident in the first 24 hours,

with disappearance of the skin manifestations. (3) Alkaline therapy, such as intravenous 5% sodium bicarbonate in 20 c.c. doses. (4) Intravenous doses of 5 to 10 c.c. of 1% tartar emetic, or other antimony preparations intramuscularly, are not much used. (5) Various substances have been used to stimulate the reticulo-endothelial system, such as urotropine, gonacrine, colloidal suspension of benzine charcoal in physiological saline (5 c.c. every 2 days), omnadin, ichthyol, pituitrin, a vaccine made from lepromas. (6) Chemical substances and dyestuffs have been used as intravenous 1% methylene blue solution in distilled water, dose 0.2; gentian violet 0.18 to 0.24 oral for adults; 1% intravenous mercurochrome. (7) A great variety of sera and vaccines. (8) Perez and Orbaneja use intravenous succinic acid, 5 c.c. daily of a 2% solution, and think that it has a cortisone-like action. The results are sometimes good, but it does not prevent relapses. (9) Chloropromazine has good results from its neuroplegic and ganglioplegic action, but has the disadvantage of being hypotensive. (10) INH in doses of 5 mgm. per kilo of body weight (about 4 or 5 tablets orally a day) has good results in 80% cases with some workers, but has failed with others. (11) Injectable Vitamin D with calcium chloride by mouth and a lacto-vegetarian diet has been recommended by Herrera and has a high percentage of good results. There are relapses. (12) Vitamin PP has given good results with Floch. (13) Irgapyrine has been used by some, but has no efficacy. (14) Cortisone acetate and ACTH. Cortisone has been used in doses of 50 mgm. six-hourly (200 mgm. in the first 24 hours, and reduced after control of the symptoms to 100, 75 and 50 mgm. daily). It acts on the connective tissues and not on the disease, and sulphone therapy can be continued during its use. The special precautions peculiar to cortisone therapy must be observed. Cases suitable for cortisone are those with intense reaction which endanger the general state of the patient. The use of ACTH is necessary in association with cortisone in order to avoid prolonged inertia and consequent atrophy of the suprarenal. It is injected in doses of 100 to 150 mgm. after 10 days of cortisone therapy. (15) Candido Silva has been making experiments in the use of biological products (see reference to his paper at an earlier stage of this Abstract). (16) Use of BCG as a desensitizer at various places in Brazil resulted in preliminary aggravation of the reactions but went on to considerable improvemtent, even accompanied in some by improvement in the general state. The BCG was given by mouth in doses of 0.2 mgm. weekly for 15 weeks, in one or more courses. The method is perfectly tolerated and is thought to be so efficient as to be part

of the solution of the problem of erythema nodosum leprosum reactions. (17) As recommended by Muir and Jeanselme, methods are applied to provoke the reactions, in the belief that they are beneficial. Muir gave 1 to 2 gm. daily of potassium iodide, increasing daily by 1 to 2 gm. up to 6 to 7 gm. If there is no reaction, the treatment is suspended. Usually a reaction begins on the second day, and the treatment is kept up for 2 weeks if there is no deterioration in the general condition. Three reaction periods can be provoked in this way in 4 to 7 months. The method seems precarious and risky.

All the above methods are tarred with the brush of empiricism. More basic research and comparative clinical studies are needed. When we do use any of the above methods, we should do so on the basis of a careful study of the course of the disease in each individual patient.

Dr. A. M. Alonso gives a careful clinical study of erythema nodosum leprosum. He says it is really an extensive polymorph erythema with associated and important involvement of nerves, joints, and certain organs, and it always calls for observation and care of the patient in hospital. Prof. R. N. Miranda points out in his paper that a positive lepromin reaction in a case of erythema nodosum will make it unlikely that it is the leprotic form. He thinks that peripheral nerves in lepromatous cases can be attacked by erythema nodosum leprosum and such cases should be called acute nodosis of leprosy.

The symposium concluded with an interesting discussion which focalized many of the aspects of the problem, and some of the points in dispute. There seemed general agreement, as Dr. P. P. de Oliveira pointed out, that the condition only appears in th lepromatous, that lepromatous cases who have erythema nodosum have a high rate of tuberculin hypersensitivity, that the incidence of the condition has increased since the introduction of sulphone therapy, that the condition often seems beneficial in the course of the disease, that leprosy is not the only factor in the appearance of the condition. Dr. H. C. de Souza-Aranjo made reference to the possible role of granules in the leprosy bacilli, which from phase-contact microscopic studies he thinks to be regenerative elements in the bacilli which have been seen to form new bacilli, and such granular bacilli are common in leprosy cases which are in regression.