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CONTENTS

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EDITORIALS

Lepra Reaction

The word " reaction " is used in different senses in leprosy. A delayed local reaction to intradermally injected purified lepromin, if it occurs in a subject who has not had previous contact with leprosy, may be counted as either natural cellular reaction to the lepra bacillus, or the result of previous sensitization by some other mycobacterium. If the subject has had contact with leprosy, or is suffering from early tuberculoid leprosy, the reaction may be enhanced, presumably because he has been sensitized by a previous infection. But if the lepromin test be applied in a lepromatous patient the reaction is negative, and naturally so; because if the millions of bacilli already in the tissues do not cause a reaction then why should the comparatively few bacilli injected do so? And yet this lepromatous patient may, for one of a dozen causes, or for no known cause at all, suddenly begin to react to the bacilli in his tissues and may react most violently. This reactive phase is generally known as " lepra reaction ". What causes it? Is it the result of sudden sensitization? If so, it is surely a very different kind of sensitization from that which sensitized the leprosy contact or the early tuberculoid case referred to above. Also a condition very similar to this naturally occurring lepra reaction may be caused equally suddenly by a sufficient oral dose of iodide; and this reaction will pass off as the iodide is eliminated from the body. If this action of iodide could be understood then it might form a key to understanding the nature of lepra reaction. Two things may be asserted about this action of iodide: (1) it is not dependent on the action of iodine, as large quantities of iodine suspended in oil can be injected without causing reaction; (2) iodide does not act directly in the tissues to cause reaction, as intradermal injections of iodide solution, sufficient to cause a high local concentration, does not cause a local reaction.

In the last few years corticotrophin and cortisone have come into use in the control of lepra reaction. It is possible that iodide acts on the endocrine system to produce effects the opposite of corticotrophin and cortisone? This seems to point to a fruitful line of investigation.

Lepra reaction is often precipitated by accompanying diseases which lower the patient's resistance; but, on the other hand, certain grave weakening conditions, such as enteric and dysentery, have the effect of suppressing reaction to the extent that nodules and other clinical signs of leprosy rapidly disappear, but appear

again generally in aggravated form as the patient recovers. This is apparently due to temporary weakening of the tissue cells to the extent that they cannot react to the bacilli in their neighbourhood. This phenomenon also requires careful investigation.

The paper by Jopling and Cochrane in this issue gives a clear exposition of the useful role of cortisone and corticotrophin in the control of lepra reaction. In earlier reports of this form of endocrine treatment dramatically effective results were recorded, but the effects were not lasting and reaction returned when administration was stopped. Also excessive doses were at first given. Later workers have shown that equally good but continuing results can be obtained with smaller doses carried on over an indefinite period. This has been confirmed by the authors of the present paper, who also find that sulphone administration does not need to be suspended during endocrine treatment, though the dose may be diminished if reaction is severe. If these findings are confirmed then it should be possible to continue sulphone treatment with less interruption, with more rapid progress, and with much greater comfort to the patient.

One difficulty at present is expense. It may be that the new synthetic steroids mentioned in this paper will be less costly in course of time. We also await further trials of phenylbutazone, favourably reported on by Destombes and Chambon (*Lep. Rev.*, July 1956, p. 136). If these are favourable we should be able to control much more effectively the most distressing of all the complications of leprosy.

VII International Congress of Leprology

The date and location of this congress are now finally fixed. It is to be held in New Delhi, India, during the week beginning the 7th of December, 1958.

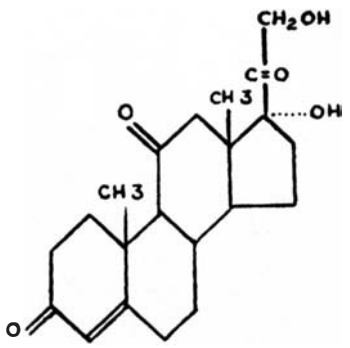
Correction

On page 139, line 4, of the last issue, " lepra " should read " lepromin ".

THE PLACE OF CORTISONE AND CORTICOTROPHIN IN THE TREATMENT OF CERTAIN ACUTE PHASES OF LEPROSY

W. H. JOPLING, M.R.C.P. (LOND. & EDIN.), D.T.M. & H.
R. G. COCHRANE, M.D., F.R.C.P., D.T.M. & H.

In 1936 a steroid was isolated from the adrenal cortex [1] which became known as compound E, and in 1949 its name was changed to cortisone. It is converted in the body into a closely allied substance, hydrocortisone, which is being continuously produced by the normal adrenal cortex as a result of stimulation exerted by the anterior pituitary gland via corticotrophin (ACTH). Although the average amount of hydrocortisone produced daily is 25-40 mg., larger supplies are required by the body when subjected to strain and stress such as trauma or major surgery. Both cortisone and hydrocortisone can be synthesized for therapeutic use, the former as the acetate and the latter either as the free alcohol or as the acetate. It is generally agreed that cortisone is preferable for systematic use and hydrocortisone for local application or for injection into joints.[2]



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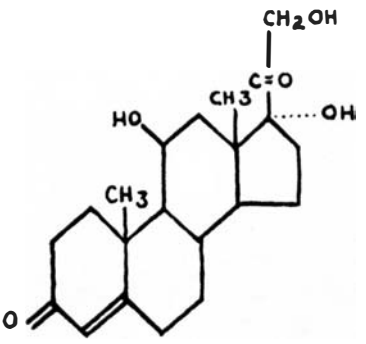
(Cortisone or Compound E)



17 hydroxy corticosterone
(Hydrocortisone or Compound F)

Corticotrophin (ACTH) is the adrenocorticotrophic hormone of the anterior pituitary gland, and its function is to stimulate production of hydrocortisone by the adrenal cortex. It is obtained for therapeutic use from the anterior pituitary glands of mammals, and has to be administered by injection.

Among the disorders in which cortisone and ACTH have a beneficial effect are certain allergic states, but their exact mode of action in suppressing or counteracting tissue reaction is as yet unknown. The physician who undertakes to treat leprosy must be prepared to treat a number of allergic complications as well, and it is important for him to know which of these will respond to

steroid therapy in order that he may relieve pain and prevent serious sequelae. These are: (1) Severe erythema nodosum leprosum; (2) Allergic reactions in the eyes; (3) Severe or persisting neuritis; (4) Acute sulphone sensitization.

Erythema Nodosum Leprosum. This is an allergic phenomenon which may occur in lepromatous leprosy (or in dimorphous leprosy which is passing into the lepromatous type) during the stage of the disease when the bacilli are becoming granular; it is not an exacerbation of the underlying disease. Thus it need not be considered an unfavourable development and will not require special treatment so long as it takes a mild form. If severe, however, and associated with complications such as high fever, prostration, mental depression, neuritis, iridocyclitis, lymphadenitis, orchitis, arthralgia and bone pains, steps must be taken to bring it under control. Some cases will respond to analgesics, antimony injections and immediate stoppage of sulphone therapy, but all will respond rapidly to cortisone or ACTH. Cortisone is put up in tablets of 5 and 25 mg., and dosage is 100 mg., on the first day (divided into three 8-hourly doses) reducing each day so long as the reaction is being controlled; e.g. 100 mg.—75 mg.,—50 mg.—25 mg.—12.5 mg. Such a 5-day course will often prove adequate but can be repeated as required. Sulphone treatment must be continued throughout, but it may prove desirable to make a reduction in dosage. One of us (R.G.C.) has had success with the less orthodox method of commencing with small doses of cortisone and increasing daily until the reaction is controlled. If ACTH is used the daily dosage will be 30-40% that of cortisone, and we would recommend a long-acting preparation which need not be injected more often than once daily (ACTH gel), the scheme for a 5-day course being 40 mg.—30 mg.—20 mg.—10 mg. 5 mg. Should the reaction not be controlled by a short course of cortisone or ACTH, then treatment must be continued for as long as required, using the smallest effective daily dosage and persevering with sulphone. The fact that sulphone treatment need not be stopped is one of the great advantages accruing from the use of these hormones, and our experience, together with a study of the literature, satisfies us that early fears of aggravating the underlying leprosy have proved unfounded. Many clinicians have reported successful results with short courses of cortisone or ACTH,[3-17] and some have used prolonged courses without ill effect.[18, 19] We have given cortisone to two patients for periods of 11 and 15 months respectively, with no adverse effect, and one

of Sir George McRobert's patients required three courses each of 4½ months. In all but short courses it is advisable to give 3-5 grammes of potassium chloride by mouth daily, to restrict salt intake if oedema develops and to treat with mercurial diuretics those in whom oedema persists. Withdrawal symptoms may occur if large doses of cortisone are stopped abruptly; these include headache, anorexia, nausea, vomiting, restlessness and joint pains, but will subside in 2-5 days.[20] Such symptoms are due to temporary cortical atrophy, and in order to prevent them it is necessary to make a gradual and progressive reduction in dosage towards the end of the course of treatment in order to allow time for the patient's adrenal cortex to recover. Should a situation arise in which cortisone had to be stopped abruptly it would be advisable to give a few injections of ACTH to stimulate endogenous cortisone production. If major surgery has to be carried out while a patient is having prolonged treatment it is important to give additional cortisone to cover the immediate post-operative period, for the patient's adrenals will not be able to produce the extra hydrocortisone which is normally secreted at this time and dangerous adrenal insufficiency may arise. The patient's requirements will be covered by 300 mg. of cortisone on the day of operation and on the first postoperative day, dosage being gradually reduced thereafter to the preoperative level. On the day of operation it is best administered as a continuous intravenous drip of 100 mg. in 1500 ml. of 5 per cent dextrose in water every eight hours. If ACTH gel is given over a long period it will be found possible to reduce the frequency of injections from once daily to once every other day and even to twice a week, and, unlike cortisone, it will not produce cortical atrophy. As it depends for its effect on the functioning capacity of the patient's adrenal cortex a poor response is likely if the latter be damaged or diseased, and this is important in lepromatous leprosy for the adrenal glands may undergo amyloid change[21] with subsequent inability to respond fully to stimulation by ACTH.[22] In addition, it tends to cause greater salt and water retention than cortisone, has more marked androgenic effects, and in rare instances may give rise to serious sensitivity reactions.[23]

There is no evidence of acquired drug resistance or of addiction to cortisone or ACTH,[24] and contra-indication to their use are few. Active tuberculosis is one, but we know of a patient with pulmonary tuberculosis and lepromatous leprosy in whom the lung lesion healed radiologically during a 6-month course of cortisone which was given to control severe erythema nodosum

leprosum. The patient received streptomycin and isoniazid throughout this period. Another contraindication is said to be present or past mental illness, but doubt has been cast on this view.[25] Caution should be observed in severe hypertension and in congestive cardiac failure (sodium and water retention), in peptic ulceration and diverticulitis (silent perforation), in a patient who gives a history of previous thrombo-embolic episodes (decreased clotting time), in diabetes (increased glycosuria) and in severe osteoporosis (increased protein catabolism). In osteoporosis it would be wise to prescribe testosterone and a high-protein diet.

Recently two new synthetic steroids have been marketed, namely, prednisone and prednisolone, which are analogues of cortisone and hydrocortisone respectively and are 3-5 times more potent. They are put up by various manufacturing chemists in 5 mg. tablets, and the maximum daily dose should not exceed 40 mg. They have the advantage of not causing sodium retention or potassium depletion, but other side-effects are not lessened and gastric disturbance is more likely to occur. Dosage during a 5-day course would be: 20 mg.—15 mg.—10 mg.—5 mg.—2.5 mg.

Iritis, Iridocyclitis and Scleritis. Any or all of these allergic reactions may occur in lepromatous leprosy either during an erythema nodosum reaction or independently, and require energetic treatment with eye-drops of 1% hydrocortisone acetate or cortisone acetate. The drops should be instilled hourly in the acute stage, gradually decreasing to a maintenance dose of thrice daily, and a 2½% ointment is useful for application at night. Atropine drops may be required in addition. Systemic treatment with cortisone or ACTH will rarely be required but should be instituted if the drops fail to control the attack within 24-48 hours.

Severe or Persisting Neuritis. Unlike eye reactions, neuritis is not confined to lepromatous leprosy for it is not uncommon in dimorphous and tuberculoid leprosy under sulphone treatment. In the lepromatous type it is usually associated with erythema nodosum reaction but may occur independently. Oedema is the factor responsible for nerve swelling and pain, and, if unrelieved, will cause ischaemia and other pressure effects owing to the limited expansile capacity of the nerve sheath. This situation calls for speedy action, particularly when the common peroneal or ulnar nerves are involved, in order to prevent complications such as dropped foot or claw hand. The first line of action is to stop sulphone and to give an intraneural injection of 1-2 ml. of

equal parts of 2% procaine and a suspension of hydrocortisone 25 mg. per ml. Such injections should be repeated as often as required for they combine the analgesic action of procaine with hydrocortisone's function of relieving oedema and inhihibiting fibrosis. Garrett[26] has advocated a combination of hyalase with procaine and injects 5-6 ml. at a sitting, and on the strength of his results it would be worthwhile assessing the value of hyalase combined with hydrocortisone and procaine, but it is possible that the spreading action of hyalase will be nullified by hydrocortisone's anti-hyaluronidase effect. Treatment by intraneural injections may in some cases require to be supplemented by systematic cortisone or ACTH, but surgical treatment should be instituted without delay if progress is not satisfactory and the function of a vital nerve is threatened. Nerve swelling in tuberculoid leprosy may be due to caseation, and, if this is suspected, surgical treatment should be carried out and hormone treatment avoided.

Acute Sulphone Sensitization. Cortisone and ACTH have a very important place in the treatment of severe sulphone sensitization and have radically improved the prognosis in this dangerous and even fatal complication. Dosage will depend on response, but the following daily dosage scheme is suggested as a basis: **cortisone,** 200 mg.—175 mg.—150 mg.—125 mg.—100 mg.—75 mg.—50 mg.—25 mg.—12.5 mg.; **prednisole or prednisolone,** 40 mg.—35 mg.—30 mg.—25 mg.—20 mg.—15 mg.—10 mg.—5 mg.—2.5 mg.; **ACTH,** 80 mg.—70 mg.—60 mg.—50 mg.—40 mg.—30 mg.—20 mg.—5 mg.

In mild cases, where systematic treatment is not required, dermatitis and associated pruritus can be treated by an ointment containing hydrocortisone or prednisolone at strengths of 1 or 2½ per cent.

Summary and Conclusions

We have given a short account of cortisone and corticotrophin (ACTH), together with their side effects, and have described their important role in the treatment of certain allergic complications of leprosy. Severe erythema nodosum responds dramatically to these hormones, and one or two short courses are often sufficient to bring the reaction under control. Prolonged courses may be necessary in some cases, even up to twelve months or more, and have the great advantage of enabling sulphone treatment to be continued without interruption. We are satisfied that patients who have been so treated have not suffered any aggravation of their underlying

leprosy. Details of management are given and mention is made of the new synthetic steroids prednisone and prednisolone. An account has also been given of the importance of steroid therapy in the management of acute ophthalmic and neural reactions, and, lastly, of severe sulphone sensitization.

It is concluded, therefore, that there is a definite place for the use of cortisone and corticotrophin in certain acute complications of leprosy and of sulphone therapy, not only for the relief of distressing symptoms but also for the prevention of lasting disability.

Acknowledgements

Grateful thanks are due to Sir John Taylor of the Medical Research Council for supplies of cortisone and ACTH for use at the Jordan Hospital, and to Dr. Gladys L. Hobby of Messrs. Chas. Pfizer & Co. Inc. for supplies of " deltacortril ". We would also like to thank Sir George McRobert for permission to include details of one of his patients.

REFERENCES

1. MASON, H. L., MYERS, C. S. and KENDALL, E. C. (1936). J. Biol. Chem., 114, 613.
2. COPE, C. L. (1955). Practitioner, No. 1049, Vol. 175, 540.
3. ROCHE, M., CONVIT, J., MEDINA, J. A. and BLOMENFELD, E. (1951). Internat. J. Leprosy, 19, 137.
4. MELSOM, R. S. (1952). Ibid., 20, 195.
5. LOWE, J. (1952). Brit. Med. J., 2, 746.
6. DE SOUZA-ARAUJO, H. C. (1952). Folha Méd., 33, 202; also, Brasil-méd., (1953), 67, 83.
7. DHARMENDRA (1953). Leprosy in India, 25, 123. Reprinted in Internat. J. Leprosy (1953), 21, 201.
8. GAY PRIETO, J. (1953). Internat. J. Leprosy, 21, 581.
9. ARGUELLES CASALS, D. (1953). Bol. Soc. cubana Derm. y Sif., 10, 23.
10. DORENLOT, H. (1953). Bull. Soc. Path. exot., 46, 56.
11. IGLESIA, M. H. (1954). Rev. Asoc. Med. Argentina, Vol. 68, Nos. 769/70, 55.
12. FARRIS, G. (1954). Arch. Maragliano Path. e Clin., 9, 1135.
13. MONTESTRUC, E. (1954). Bull. Soc. Path. exot., 47, 848.
14. CONTRERAS, GUILLEN, MIGUEL, S., TERENCIO and TARABINI (1955). Rev. " Fontilles ", Vol. 3, No. 8, 555.
15. MAGALHAES, M. J. C., BARBOSA, A., and BASTO, P. M. (1955). J. méd. Porto, 27, 419.
16. PRIETO LORENZO, A. (1956). Med. Colonial, 27, 227.
17. DREISBACH, J. (1956). Personal communication.
18. MONTESTRUC, E. (1955). Bull. Soc. Path. exot., 48, 631.
19. DEL POZO, E. C., GONZALEZ-OCHOA, A., RICO VENEGAS, S., MARTINEZ-BAEZ, M., and ALCAREZ, M. (1955). J. Invest. Dermat., 24, 51.
20. HENNEMAN, P. H., WANG, D. M., IRWIN, J. W., and BURRAGE, W. S. (1955). J. Amer. med. Ass., 158, 384.
21. POWELL, C. S. and SWAN, L. L. (1955). Amer. J. Path., 31, 1131.
22. ZIRILLII, L., and ABATE, A. (1953). Ann. italiani Derm. e. Sif., 8, 254.
23. Annotation in Lancet (1956), 2, 666.
24. GOLDSMITH, W. N. (1955). Practitioner, No. 1049, Vol. 175, 569.
25. LEWIS, A., and FLEMINGER, J. J. (1954). Lancet, 1, 383.
26. GARRETT, A. S. (1956). Leprosy Review, Vol. 27, No. 2, 61.

RELATIONSHIP OF LEPROSY TO TUBERCULOSIS*

E. MUIR, M.D., F.R.C.S. (EDIN.)

In recent years two important conferences on tuberculosis have been held in London, in which the subject of leprosy was included in the programme. One of these was the Ciba Foundation symposium on *Experimental Tuberculosis, Bacillus and Host* in October, 1954, and the other was the *Fourth Commonwealth Health and Tuberculosis Conference* in June, 1955. Although in these conferences leprosy naturally occupied a very minor place, yet the fact that leprosy should receive this attention in a country where it is not an endemic disease is significant of the broader outlook on mycobacterial diseases.

There are many aspects from which we can view the relationship between leprosy and tuberculosis, so many in fact that it is possible in this paper only to review them discursively, drawing attention to the resemblances and divergencies of the two diseases, and the ways in which the study of the one has thrown light upon the study of the other.

In modern times leprosy has been looked upon as a tropical disease, but it is not so in any true sense. Till recently it was endemic in such cold climates as those of Iceland and Norway, and up to 3 or 4 centuries ago it was common in England and other countries of Western Europe. The sanitary, social and economic conditions which encourage the spread of leprosy have in recent years been ameliorated in Western Europe, but not to the same extent in many tropical and subtropical countries.

Sanitary, Social and Economic Advance

There are certain diseases which appear to belong to various stages in sanitary, social and economic development. Among these are notably yaws, leprosy, tuberculosis and possibly cancer, which, although they overlap each other, appear, reach their peak and again diminish in that order. Speaking generally, yaws is a disease of tribal life, common in primitive and more or less isolated communities. As communications improve, but sanitation lags behind, yaws diminishes and leprosy, a disease of villages, takes its place. As tuberculosis penetrates the community leprosy tends to die out; and again, as tuberculosis comes under control, cancer takes its place as the chief public health problem.

The replacement of yaws by leprosy is dependent (apart from the effects of modern treatment) chiefly on social and economic

* Paper presented at the conference on Tuberculosis and Leprosy, Dar-es-Salaam, Tanganyika Territory, January, 1957.

causes. The disappearance of leprosy as tuberculosis advances, though governed partly by social and economic causes and by improved sanitation, may also have immunological implications; but these will be discussed later. The apparent replacement of tuberculosis by cancer may depend on the rising age level of the community, and possibly on other factors such as the mechanisation connected with modern life.

Bacteriological Relationship

The causal organisms of both leprosy and tuberculosis belong to the genus of mycobacteria. Hansen in 1874 first described rod-like bodies in leprous nodules; but lacking suitable stains his descriptions were defective. Later, about 1879, the new staining methods of Weigert and Koch, with advice on their use by Koch, made it possible for Hansen (and about the same time Neisser) to confirm this discovery and describe *M. leprae* more in detail. *Myco. tuberculosis* was discovered by Koch some three years later, in 1882. Thus these two organisms were closely connected from their first appearance.

The whole range of mycobacteria has been likened by Hanks to a continuous spectrum, beginning at the lower end with saprophytes and ascending through commensals and intermediate forms to those which, like *Myco. tuberculosis*, are pathogenic and are yet cultivable *in vitro* and have a variety of animal hosts. Next in order comes Johne's organism which has certain particular *in vitro* growth requirements, and whose hosts are restricted to cattle and sheep. Then there is *Myco. lepraemurium* whose known hosts are restricted to rats mice and hamsters, and which is not yet cultivable *in vitro*. Lastly, at the top of the spectrum is *Myco. leprae*, also not cultivated *in vitro*, and confined to one host—man. In this series the increasing restrictions in living hosts and *in vitro* culture are connected with retirement from the open tissues of the host into intracellular life. Hanks points out that the tendency towards intracellular retirement is characterised by limited ability to gain energy from substrates *in vitro* and by susceptibility to tissue derivatives and serum. Survival in cells is associated with low oxygen requirements. Is there any connection between this and the freedom of the lungs from leprosy?

Hanks also points out that another difference between saprophytic and pathogenic mycobacteria lies in certain lipids contained by the latter, which act on the leucocytes to prevent their migration. Virulent strains of *M. tuberculosis* give off the " cord factor " (mycolanoic acid) which causes a type of local inflam-

mation, prevents phagocytosis and produces a medium where the mycobacteria can multiply.

In leprosy the relation of the infective organism to the phagocytic cell is somewhat different. When *M. leprae* are ingested by macrophages, one out of three things occurs, depending on the degree of resistance of the host: (a) if resistance is strong epithelioid cells are actively formed from the phagocytes and the bacilli are destroyed; (b) if resistance is weak the bacilli multiply in the cytoplasm, forming the large typical lepra cell, which later, as bacilli die and decompose, becomes the foamy cell often associated with the name of Virchow; (c) there seems to be evidence that between these two extremes, in both of which the phagocyte is immobilised, there may be a third possibility in which the cell after ingesting bacilli still remains mobile, at least temporarily, and may convey the bacilli through the tissues. It may be supposed that in the second of these occurrences (lepra cell type) there is some substance contained in and given off by the bacilli which paralyses the cell and makes it take up a passive role: whereas in the first occurrence (epithelioid cell type) either this substance is absent or is countered by the cell, which is thus able to destroy the bacillus.

Besides its intracellular breeding place, *M. leprae* has another place of refuge to which it invariably seeks to resort, namely the peripheral nervous system. In this respect it differs from all other known bacteria. It enters the fine cutaneous twigs and spreads upwards into larger branches and thence into the mixed nerves. Thus the cellular multiplication, which the presence of the bacilli calls forth, exerts pressure on both sensory and motor nerve fibres, resulting in their temporary blocking or permanent destruction.

There is evidence by the use of special methods of staining that *M. leprae* can enter the axons: whether or not it can travel up the nerves inside the axons there is no direct evidence, and it would seem more likely that upward progress is made through the lympth spaces along side of, but outside, the axons.

One of the contrasts between the tuberculosis group and the leprosy group of mycobacteria is found in the restrictions of experimental transmission in the latter group. Transference of rat leprosy infection is restricted to rats, mice and hamsters; with human leprosy animal inoculation has failed, and even the few recorded attempts at transmission to human volunteers have given negative or doubtful results. Unsuccessful attempts have been made in monkeys, rats, guineapigs, rabbits, hamsters and other animals. Expense and other difficulties have prevented attempts

in anthropoid apes. Recently Feldman has suggested that it may be possible to reproduce the disease by injecting the inoculum intradermally instead of subcutaneously, by lowering the resistance of the experimental host by suppressing its endocrines, or by injecting various substances which will enhance the virulence of *M. leprae*. It would appear, however, that the possible host must be fairly long-lived, as in man leprosy may take many years to develop.

Myco leprae also contrasts with *Myco tuberculosis* in our failure to cultivate the former *in vitro*. Repeated claims of successful cultures of *M. leprae* have been made in the last 50 years, but none of them has been substantiated. More recently, in place of the frontal attack on this problem, a flank assault has been launched by studying *Myco lepraemurium*, which has the advantage that any doubtful cultures can be tested in cheap and easily handled experimental animals. Hanks and others are studying the viability of these mycobacteria in various environments by means of respiration and hydrogen-transfer tests. The burning of hydrogen is a requirement of life, and therefore can be used as an indication of changes in metabolism.

Immunology

When we study the question of resistance in leprosy and tuberculosis the problems are no less difficult to solve. Yet this is the field in which possibly the two diseases impinge most closely. Calmette, who had lived in Belle-Isle in the west of Brittany, is reported as saying in 1905 that up to 50 years previous to that year leprosy had been common in Brittany. As long as leprosy remained, pulmonary tuberculosis was unknown: but after leprosy disappeared pulmonary tuberculosis ravaged the country, chiefly affecting the parts formerly occupied by leprosy. The registers of Belle-Isle bore out this assertion. Perhaps it would be better to say, not that with the passing of leprosy tuberculosis came, but that with the coming of tuberculosis leprosy departed.

There is much evidence to suggest that cross-immunity between tuberculosis and leprosy is, at least in part, responsible for the disappearance of leprosy as an endemic disease from England and other countries of Western Europe about 300 years ago, at a time when sanitation was still very bad. Also segregation laws at that time, though locally in existence, were not effectively applied and could not account for the more or less sudden vanishing. Leprosy lingered on longest in distant corners like Cornwall,

Shetland and Orkney in the British Isles, and the fiords of Norway, places where tuberculosis was slow in penetrating.

There is no test in leprosy, corresponding to the tuberculin test in tuberculosis, to give an indication of past contact with infection. The lepromin test (made by intradermal injection of a sterilised suspension of triturated leproma) gives positive results in the resistant forms of leprosy, but also in a considerable number of those who have had no contact with leprosy. The lepromin reaction is specific only when it is negative, which almost always occurs in the severe lepromatous type. Its chief use is in prognosis, which tends to be favourable when the reaction is positive, as it is almost invariably in the tuberculoid type. Further evidence of the relationship of leprosy with tuberculosis is shown by the fact that vaccination (whether oral or intradermal) with BCG converts a negative into a positive lepromin reaction in a large majority of cases. The important question at issue is whether a positive lepromin reaction induced in this way has the same significance as a positive reaction found ordinarily in the tuberculoid type of leprosy. We have no adequate proof yet that this is so, and proof that BCG vaccination raises resistance to leprosy can be arrived at only by long-term controlled trials, extending over a period of years. It is important that where BCG is being used for immunisation to tuberculosis in areas where leprosy also is endemic, arrangements should be made for combined controlled trials to ascertain the effect of BCG in raising resistance to leprosy.

The question has been raised as to whether infection with leprosy causes cross-sensitivity to tuberculosis. Edwards and Palmer suggest that in certain countries (India, Egypt, etc.) there is a non-specific factor which causes a low-grade sensitivity to tuberculin. Lowe and Mcfadzean found similar evidence in Nigeria. The Chronicle of WHO also, during a campaign of BCG vaccination in East and in West Pakistan, found a striking divergence of tuberculin results in these two areas. In West Pakistan there were doubtful reactions in only 4 per cent of the total: while in East Pakistan they were much more frequent (about 40 per cent). In fact in the latter area the presence of non-specific sensitivity would seem to limit considerably the use of the tuberculin test. As leprosy is much more frequent in East than West Pakistan the question might be raised as to whether this non-specific agent may not be leprosy, at least in part, though another possibility might be the presence of non-pathogenic mycobacteria in the body.

Clinical and Pathological Contrasts

One of the most striking contrasts between tuberculosis and leprosy lies in the difference between the organs and tissues which each attacks. The lung, which is the most important organ affected by tuberculosis, is entirely exempt in leprosy, even though the latter attacks the whole of the rest of the respiratory tract as far down as the large bronchi. Conversely, tuberculosis leaves the upper respiratory passage alone except for infection of the larynx caused by constant coughing up of bacillus-laden sputum. Unlike tuberculosis, leprosy does not affect directly the gastro-intestinal system and the kidneys, though these are indirectly affected by waxy degeneration as a result of prolonged and massive infection and septic complications. The testis is the only internal organ to be attacked and destroyed, and this is possibly connected with gynecomastia, a not uncommon complication in leprosy. The liver may be the site of a gross infection, but this seldom causes any proportional, or indeed any serious, interference with function, except when there is secondary amyloid degeneration.

The skin is the organ in which tuberculosis and leprosy have most in common. While with few exceptions all forms of leprosy affect the skin, it is the tuberculoid type which most closely resembles cutaneous tuberculosis, both clinically and histologically. In both of these, and also in Boeck's sarcoid, there is the tubercle formation of epithelioid cells often accompanied by giant cells. In all of these three conditions the process may go on to caseation, though in tuberculosis this is commoner in the lymph nodes, and in leprosy it is commoner in the larger affected nerves.

A remarkable feature of leprosy in the skin is the absence of scar formation after healing takes place. There is seldom the loss of tissue and deep scarring so often occurring in tuberculosis. In spite of the whole thickness of the skin having been affected, there remains in a healed lepromatous lesion only the wrinkled " crushed tissue-paper " appearance without any tightness. This is due to the kind of tissue which replaces the granuloma, and its nature is worthy of careful study.

Clinically and histologically the chief feature which distinguishes tuberculoid leprosy and tuberculosis of the skin is that in the former the cutaneous nerves are affected, as may be seen in biopsy sections and, clinically, by testing the tactile and other forms of sensation. Some forms of tuberculous cutaneous lesion (as also sarcoid) resemble lepromatous leprosy in which loss of sensation may be slight or nil; but these can easily be distinguished from leprosy by the absence of acid-fast bacilli.

The eyes are affected in both lepromatous leprosy and tuberculosis. In both there is interstitial keratitis; but while tuberculous keratitis causes loss of tissue and ulceration, lepromatous leprosy, spreading from the sclera over the upper limbus, causes a diffuse corneal opacity or nodulation. Ulceration of the cornea occurs chiefly in tuberculoid leprosy due to want of protection following lagophthalmia and paresis of the muscles of the eyelids. In both diseases there is irido-cyclitis, but invasion of the choroid, commoner in tuberculosis, seldom occurs in leprosy.

Invasion of the bones, especially the cancellous tissue, is common to both diseases. In lepromatous cases during lepra reaction this results in extreme pain in the ends of the larger long bones, but it is as a rule only in the smaller bones of the fingers and toes that destruction takes place, and that is generally secondary to neural destruction rather than to invasion of the bones themselves.

Nowhere is the contrast between leprosy and tuberculosis more striking than in the nervous system. As in the respiratory system, the two diseases seem to have divided the territory between them, allotting the central portion of the nervous system to tuberculosis, and the peripheral to leprosy. Apart from its resistance to culture outside the human body, the most characteristic feature of *Myco. leprae* is its affinity for the peripheral nerves, and it is possibly this neurophilic faculty which preserves it from extinction. This is illustrated in the typical ring-shaped tuberculoid lesion in the skin. The infection seeks to invade the surrounding skin, spreading from the initial focus radially through the neuro-vascular plexus. It is, however, resisted by macrophages (epithelioid cell formation) which its presence has called into action. The site of this resistance is indicated clinically by the raised, expanding, ring-shaped margin; and the success or otherwise of the resistance is determined by whether or not this expanding margin is halted or continues to widen. But the infection has a second line of advance, by entering the cutaneous nerves and spreading up them to the larger branches and mixed nerves. Similar resistance takes place in the nerves to that in the skin, which is shown clinically by the thickening and tenderness of the affected nerves. Both in skin and nerve the epithelioid tubercle formation is the same, but the process more frequently goes on to caseation and abscess formation in the nerve than in the skin. The analogous lesion in tuberculosis is the chronic brain abscess.

In the lepromatous form of leprosy also the nerves are

invaded, and to a much more massive extent than in the tuberculoid, as there is infinitely less resistance and tissue reaction. Consequently thickening and tenderness of nerves are absent or much less. If tubercular meningitis be taken as the counterpart of lepromatous nerve invasion, the mildness of *Myco. leprae* compared to *Myco. tuberculosis* is well brought out. It is only during lepra reaction that a similar acute condition is found.

To sum up, there are two outstanding differences between the natures of leprosy and tuberculosis. In tuberculosis the type of disease depends partly on the strain of bacillus, and partly on the resistance of the host. In leprosy there is no indication of differing strains, and the two main types depend entirely on the resistance of the patient. The other main difference between the two diseases lies in the nature of the reaction of the bacillus to the phagocytic cell. In tuberculosis the typical virulent bacillus makes a frontal attack, paralysing the cell and forming an extracellular medium in which the bacillus can multiply. In leprosy, in its typical lepromatous form, the bacillus lets itself be ingested by the cell and then from inside, like the malarial plasmodium in the erythrocyte, settles down and multiplies. Thus the acute tubercular lesion is typified by tissue destruction, the severe leprosy lesion by granuloma, either diffuse or nodular.

Therapeutics

It was experimental work on tuberculosis that first pointed the way to the trial of sulphones in leprosy. The result of these trials has transformed the prognosis of leprosy, and in addition to the benefit to the individual patient there is reason to believe that the wise use of sulphones may do much towards bringing leprosy under final control. Still the sulphones, though a great advance on previous treatment, have certain drawbacks in the form of toxicity, causation of lepra reaction (erythema nodosum) and particularly the long period required to remove infection. In seeking for still better therapeutic agencies, it is to clinical and experimental tuberculosis, as well as to experimental work on other mycobacteria such as *Myco lepramurium*, that leprosy workers turn for further pointers. More than pointers there cannot be, as is seen from such variances as the following: sulphones are useful in experimental tuberculosis and leprosy, but not in clinical tuberculosis or rat leprosy; INH is valuable in clinical tuberculosis and rat leprosy, but of little or no value in human leprosy.

of drug resistance.

Efforts are in hand to discover a less toxic drug, with more rapid action, especially in clearing up infection and rendering the patient noninfective.

Epidemiology and Control

If, as has been suggested by some writers, the tuberculization of a community, either by natural spread of infection or by the use of BCG or similar forms of vaccination, raises resistance to leprosy sufficiently, then it might be possible to tip the balance of the struggle between *M. leprae* and the community so that a continuous process of diminishing infection is set up.

At many centres, especially throughout the tropics and subtropics, investigations are on foot to estimate the effect of BCG vaccination on resistance to leprosy, and to study evidence of cross sensitisation between *M. leprae* and *M. tuberculosis*. There is urgent need to collect, correlate and study reports of what has already been done along these lines, and to plan on a wide international basis the steps that should be taken in further investigations.

Meanwhile, efforts at control of leprosy by providing widespread facilities for treatment should be pressed forward, due arrangements being made for training of personnel, and providing for adequate supervision. Formerly, chief stress was laid on isolation of the patient with leprosy much more rigorously than the patient with tuberculosis. Now with clearer knowledge and better tools, while not neglecting to isolate the patient as much as practicable, the chief stress should be laid on early diagnosis and on early and adequate treatment.

LEPROUS NERVE ABSCESS: REPORT OF TWO CASES

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Leprous nerve abscesses, or " cold abscesses " associated with tuberculoid (or, more rarely, with lepromatous) leprosy, have long been recognised as a rare complication of the involvement of a major superficial nerve trunk or a principal branch.[1] The incidence is variable, being fairly common in India, and distinctly uncommon in tropical Africa.

In twenty years' practice in an area of high leprosy endemicity in Belgian Congo, the writer has encountered two cases of leprous nerve abscess in a series of upwards of ten thousand cases of leprosy personally examined.

Case Reports

Case 1

An apparently healthy, well-developed Bantu woman of about 40 years of age, presented herself at hospital complaining of a painless tumour in the region of the left elbow. The history was vague: a small painless lump had been noticed in that situation some months previously, just above the elbow on its inner aspect. There was coincidentally some tingling along the ulnar border of the left hand, and in the ring and little fingers. The swelling had been increasing gradually in size, until it had interfered with her gardening work. She did not complain of any other symptoms.

On examination, an ovoid cystic swelling was present on the inner border of the left arm and forearm, posterior aspect, in the neighbourhood of the elbow joint. Its long axis measured 4½in. (11 cm.), and its short axis 2½in. (6 cm.). The skin surface was regularly smooth, as was the surface of the tumour; the tumour itself was not attached to the skin, which moved very freely over it. It was attached deeply, probably throughout its entire length. The swelling was uniformly cystic, and appeared clinically to consist of a single thin-walled sac containing liquid. The skin was of the same temperature as elsewhere.

A large inactive tuberculoid macule covered the outer aspect of left arm and forearm, enclosing the elbow. The centre was normally pigmented, but of the appearance that suggested an old healed minor tuberculoid lesion—small, smooth, shiny plaques of atrophic skin, separated by shallow furrows. The periphery of the macule was slightly raised and pebbly, but presented no

clinical evidence of activity. The process of flattening, re-pigmentation and cicatrization was proceeding here and there along the periphery, i.e. the lesion was becoming a healed tuberculoid macule, the process being more advanced inferiorly, where the lesion faded indefinitely into skin normal in colour and texture.

The little and ring fingers were slightly flexed, and active full extension was impossible. The nail bed of these two fingers was shiny and atrophic; the fingers themselves were slightly more pointed than the remaining unaffected fingers. No trophic ulceration was present. Complete anaesthesia to cotton wool was present along the ulnar border of the hands, and on the ring and little fingers, with dulled appreciation of pin-prick and absence of tactile discrimination and temperature sense.

Bacteriological examination by standard methods of the least inactive portion of the edges of the macule (i.e. superiorly and externally) gave negative results for *M. leprae*.

Operation

Under brachial block anaesthesia (20 ml. of 1% procaine) an incision was made over the most prominent aspect of the swelling. The very thin adhesions between subcutaneous tissue and cyst wall were easily broken down by gauze dissection. The cyst wall was punctured in so doing, and very freely running yellow fluid escaped.

The entire cyst was then freed by gauze dissection except on its deep aspect. As a precautionary measure, the contents of the cyst were completely evacuated to reveal the nature of the deep attachments. The ulnar nerve, swollen and red, was seen lying along the base of the cyst, and the wall of the latter was continuous with the nerve sheath. The thin wall was carefully dissected from the nerve and removed entire, the perineurium being longitudinally incised in the process. Since the nerve itself did not appear to be under tension, anterior transposition was not performed.

Areolar tissue was loosely stitched over the nerve, and the deep tissues brought together, and the wound closed with drainage. The drainage tube was removed on the second day, and the wound healed virtually by first intention.

Subsequent history

The ring and little fingers showed no improvement in spite of nocturnal splinting and remedial exercises.

Examination of the pus from the cyst by standard methods was negative for all bacteria, including *M. leprae* and *M.*

tuberculosis. The cells present were very degenerate, their nuclei scarcely taking the stain.

The subsequent history of the patient is unknown, as she cannot be traced.

Case 2

A Bantu schoolboy of 14 years of age complained of a painful swelling behind the left knee of four weeks' duration. There was no history of infection via the skin, or from a wound on the foot or leg; he attributed the swelling to the fact that he had been standing in a canoe for some three days, paddling sixty miles upstream against the Congo current.

The calf muscles seemed subjectively "heavy", and numb, and the patient complained of painful paraesthesiae in calf and foot, painful sensations of heat and cold in the left foot, and painful sensations of cold first noted in the lower calf and in front of the ankle.

On examination, the left knee was held flexed, and extension was actively resisted because of pain. A diffuse tender swelling occupied the popliteal region; its borders were ill-defined, and merged into the surrounding tissues. Its centre was fluctuant. The inguinal glands of the same side were enlarged and tender. The skin over the swelling was normal in appearance, and was of the same temperature as distant skin. In particular, there was no evidence of leprosy or any cutaneous infection locally or within the drainage area of the popliteal gland. There was no excess of fluid in the knee joint, and no evidence of gonorrhoea, bacillary dysentery or tuberculosis. There was no tropical myositis in sites of predilection.

The general condition of the patient was excellent; temperature and pulse were normal, and no pathological signs were revealed on examination of the systems. The white cell count was within normal limits, and the differential count normal.

Operation

Under chloroform anaesthesia, a longitudinal incision 4in. long was made over the swelling, and the subcutaneous tissues were incised. Gentle dissection of the oedematous wall of the abscess cavity superficially, disclosed a mass about 4in. (10 cm.) long, and 2in. (5 cm.) in breadth at its widest. The tense wall was incised, releasing about 40 ml. of moderately thick yellow pus. The cavity was explored with the gloved finger, and several fragile bands broken down. When all the pus had been evacuated, and

the cavity flushed with 1/1000 aqueous acriflavine solution, the walls were examined. Running longitudinally along the floor, appearing superiorly in the apex of the popliteal space, was the red and swollen popliteal nerve. The popliteus muscle was intact, and no lymphatic glands were seen. The sheath of the nerve was incised in the direction of its fibres, and the nerve itself freed with the finger from the recent adhesions to its bed.

The wound was closed with drainage, and the leg splinted in 10° of flexion.

Subsequent history

Examination of the pus by standard methods revealed very degenerated white cells, and disclosed no bacilli colorable by methylene blue, Gram's stain, or Ziehl-Neelson's stain.

The operation wound healed with slight superficial secondary infection, and the local pain behind the knee disappeared completely. The pain and paraesthesiae in the leg below the knee persisted, and within a few months of discharge from hospital, the patient noticed weakness in his left foot and early foot-drop.

Complete clinical and bacteriological examination still revealed no sign of leprosy.

Shortly afterwards, he developed a typical tuberculoid macule embracing the left knee and encroaching on the lower third of the thigh and below the head of the fibula; the extensive lesion appeared rapidly, not increasing gradually and centrifugally from a small papular tuberculoid macule as is the more common mode hereabouts. The whole area involved became uniformly hypopigmented; the border was slightly raised and papular, active and succulent.

The evidence of nerve involvement was furnished by the typical combination of wasting of the calf muscles, foot-drop and trophic ulceration of the first and fifth (left) toes. Examination of cutaneous and deep pressure, sensation and temperature sense, provided confirmatory evidence.

Further widespread tuberculoid lesions made their appearance within the next few years—on shoulders, right cheek, trunk. In the absence of cutaneous involvement on the right leg and thigh, signs of nerve complications became apparent, followed many months later by tuberculoid lesions similar to those on the left thigh and leg.

Meanwhile, the patient had been treated with standard doses of Dapsone (which had by that time become available), with good

clinical results as far as the cutaneous lesions were concerned. The results of nerve involvement remained unchanged.

Comment

Both cases concern the appearance of a bacteria-free collection of pus in association with a major nerve trunk near an articulation.

In the first case, an extensive tuberculoid macule undergoing spontaneous retrogression, involved the skin overlying the abscess and beyond. In the second case, no cutaneous lesion was present at the time, but an extensive minor tuberculoid macule appeared subsequently, involving a widespread area of skin in the vicinity of the abscess.

In both cases, the nerve trunk was the seat of an oedematous inflammation, and signs and symptoms of motor and sensory involvement were present when the abscess cavity was evacuated. In the first case, the nerve involvement had been present some months; in the second, it appeared *pari passu* with the developing abscess.

In each case, incision of the nerve sheath was performed too late to reverse the changes due to compression of the nerve fibres.

In the first case, a long-standing collection of pus was enclosed in a definitely walled thin sac; in the second case, subacute rather than chronic, the abscess wall was thick, soft and oedematous, and less well-defined. The first sac was removed easily, complete; the second had to be left *in situ*, so closely was it adherent to adjacent tissues.

After evacuation of the pus, the wounds healed without difficulty, and with only superficial infection. In both cases, the pus contained no organisms demonstrable by standard methods of examination.

Summary

Two cases of leprous nerve abscess associated with main nerve trunks in cases of tuberculoid leprosy are reported from the Belgian Congo. In one case, the tuberculoid lesion was long-standing and quiescent; in the other, cutaneous lesions had not made their appearance at the time the abscess was forming, but appeared later.

1. ROGERS, L., and MUIR, E. (1946). Leprosy, 3rd Ed. John Wright & Sons Ltd., Bristol.

REVIEWS

International Journal of Leprosy, Vol. 24, No. 1, Jan.-Mar. 1956.

K. Kitamura and M. Nishiura write on *Classification of Leprosy in Japan.* A symposium on this subject was held at the 28th annual meeting of the Japanese Leprosy Association. Four questions were put forward and answered:

(1) Should the neural type be maintained as one of the main types of leprosy? The general opinion was that cases which have nothing other than neurological syndromes and/or anaesthetic hypochromic macules should be brought together either as a type or subtype.

(2) Is the indeterminate group necessary as a clinical unit of leprosy? About this there was some absence of unanimity, but there was a tendency to regard this as a stage (passing from one of the two main types to the other) rather than as a fixed group or type.

(3) Is the borderline group necessary as a clinical unit of leprosy? The majority considered it unnecessary, but four of the fourteen speakers considered it was necessary, to include cases passing from tuberculoid to lepromatous, and also those passing in the other direction.

(4) An acute infiltration condition was described, being a syndrome with erythematous infiltrated skin lesions, with fever of 37-39° C. and joint pains, " all occurring acutely either in an early phase of lepromatous leprosy, or in the absorption period ". It differs from ordinary lepra reaction, and sections reveal tuberculoid structure with coexistence of lepra cells. The Mitsuda reaction tends to change from negative to weakly positive. [This seems to be what most workers would call the " borderline " group.]

Dr. Kitamura points out that the classification of leprosy is influenced by general ideas of medicine at the time when the problem is discussed. Especially in the last decade or two it has become more and more complicated by accepting from the immunobiological and pathological points of view various transitional and intermediate forms. There is no doubt that clinical manifestations of leprosy differ under various geographical and racial conditions. It was hoped that the symposium would be of use in drafting a universally acceptable classification at the international congress to be held in India in 1958.

R. V. Wardekar gives a *Preliminary Report on the Data of the Control Units of the Gandhi Memorial Leprosy Foundation,* which is

a progress report of work begun in 1951. Ten leprosy control units have now been established. In locating these all over India, variations in diet, customs, etc., have been represented. They are supervised regularly by a trained worker. Each unit covers an area of 3 to 5 miles radius and a population of 15 to 26 thousand; it contains 2 or 3 clinics according to the population. The incidence of leprosy found varies from 1 to 6 per cent. Details are given of the unit at Sevagram, the first to be started and the centre from which the others are supervised. The area is surveyed and resurveyed, and an attempt is made to survey at least 90 to 95 per cent of the population in each period of two years. At Sevagram in 1952, 357 cases were detected and 213 registered at the clinic; in 1953 there were 17 detected and 89 registered; in 1954 there were 125 detected and 104 registered. This makes totals of 499 detected and 406 registered during the three years. Of the 499 detected cases 69 were lepromatous and 430 non-lepromatous. Of the 406 registered cases bacteriological examination showed 16.5 per cent to be infectious, and 83.5 per cent to be non-infectious. From this it was calculated that of the total detected number 82 were infectious and 417 non-infectious. The question is discussed as to whether so few infectious cases could have infected so many non-infectious ones. "If it should be proved that negative cases are infective, that would be a further obstacle to control of leprosy by chemotherapy." Much stress is placed upon examination of contacts of registered patients. Out of 618 contacts of 191 patients, 10 had leprosy, 5 of them being contacts of non-infective and non-lepromatous patients.

[This paper is worthy of careful study in the original.]

R. G. Urgarriza discusses the *Leprosy Problem in Paraguay.* Besides the 400 patients in the leprosarium of Santa Isabel there are 1,590 known cases, of which 100 are in the capital. From findings among the troops it was calculated that there are probably some 5,000 in the country. Since a visit of the WHO representative in 1950 and 1954, efforts are being made to carry out a census of leprosy, to standardize the treatment and to obtain the necessary specialists. There is a preventorium with 120 children.

J. Convit writes about his *Investigation of Leprosy in the German Ethnic Group of Colonia Tovar in Venezuela.* His paper deals with the fourth stage of an investigation into the clinical findings and changes in the Mantoux and Mitsuda reactions in 110 persons who were vaccinated with BCG in 1950. They all share quarters with lepromatous patients, and thus are placed in great danger of infection. Before vaccination with BCG all gave

negative Mitusda reactions and 100 of them negative Mantoux reactions, but in none was there any sign of leprosy. Of the 106 examined 10 weeks after vaccination 93 had converted to positive Mitsuda reactions, 58 giving 1 plus, 21 giving 2 plus, and 14 giving 3 plus. The negatives and 1 plus cases were revaccinated, some twice, and at the end of June 1955 all were Mitsuda positive. The person who failed to show for vaccination in 1950 and had remained unvaccinated showed macular lepromatous leprosy in 1953, and 3 others showed incipient tuberculoid lesions though their Mitsuda reactions were strongly positive. Since 1953 there has been no new case of leprosy in the group. In the Mantoux tests made in 1953 the number of positives had risen to 46, but in 1955 it had fallen to 31. [Indicating that in that period of time the positive conversion after BCG vaccination is more stable with the Mitsuda than with the Mantoux test.]

A. T. Roy gives the *Bacteriological Results of Treatment of Lepromatous Cases with Diaminodiphenyl Sulphone by Mouth for Periods up to Five Years.* Details of treatment with DDS in 99 lepromatous cases are given and the results after five years. As some of the patients fell out others were added, so that the length of treatment varied from 14 to 60 months, with an average of 44.5 months. During this period 9 patients became bacteriologically negative, 10 nearly negative, in 25 the bacilli diminished by 25 per cent and in 32 by 50 per cent, 19 were only slightly improved and 4 remained stationary. " It is impossible to predict from the degree of bacteriological positivity at the beginning of treatment how long it will take a case to clear up if it is to do so. Some cases with low BI [bacteriological index] took more time to become negative than cases with high BI's."

Subsequent Evolution of the Induced Mitsuda Reaction in Clinically and Bacteriologically Negative Lepromatous Cases, is the subject of a paper by S. Schujman. In 40 lepromatous cases which had become clinically and bacteriologically negative after several years of treatment, vaccination was performed with Stefansky antigen in 13, with BCG orally in 19, and with BCG intradermally in 8 cases. In none of these was there an early reaction induced, but there was a late reaction in 47 per cent of those given oral BCG, in 50 per cent of those injected with BCG, and in 69 per cent of those receiving the Stefansky vaccine These positives appeared 3 months after vaccination, but within 6 months they had again become negative. When they were again vaccinated with their former vaccines they again became positive. It was found that after the 4th month few responded, and after

the 5th month none responded. The induced lepromin reactivity in lepromatous cases has no protective value.

Leprologia

The above is the title of the official organ of the newly formed *Sociedad Argentina de Leprologia.* The Society has been formed under the presidency of the well-known leprologist, Dr. José M. M. Fernandez. There are 104 original active members (socios titulares), 18 honorary members and 11 associate members. There are also 24 corresponding members from 9 different countries. The secretary is Dr. E. T. Capurro. The first number of the journal, dated January to June 1956, contains no fewer than 17 original articles, many of which were presented at the first meeting of the society held in Corrientes on the 20th of August, 1955.

The first article, by J. M. M. Fernandez, is on the *Immunological Relationship between Leprosy and Tuberculosis.* It is summarised as follows:—

Antigens with tubercular material were prepared by the methods used for the preparation of lepromin, and the reactions provoked by them were observed in guinea pigs in the following conditions: (a) normal, (b) calmetized, (c) previously injected with the tubercular antigen. Tuberculin positive and tuberculin negative human subjects were also tested with these antigens.

Tubercular antigen (Tb), equivalent to bacillary lepromin, is a suspension of human type Koch bacilli killed by heat.

Tubercular antigen (Ti), equivalent to integral lepromin, was prepared from lymph glands of tubercular guinea pigs by the Mitsuda-Hayashi method for preparing lepromin.

In guinea-pigs, tuberculized by inoculation of dead bacilli or calmetization, (Tb) and (Ti) provoked: (a) an early reaction appearing within 48 hours, consisting of erythema and edema, similar in its aspect and course to the Fernandez reaction; and (b) a late nodular reaction, appearing between the second and third weeks, similar to the Mitsuda reaction. In normal guinea-pigs the early reaction was negative, and the late reaction was either negative or weakly positive. In guinea-pigs which had been previously injected with (Tb) or (Ti), the second injection provoked early and late positive reactions.

Tuberculin-negative subjects showed a negative early reaction, and a positive late reaction in 70 per cent of the cases. Tuberculin-positive subjects showed positive early and late reactions.

The results of the early reaction to (Tb) or (Ti) usually coincided with those of the Mantoux test. The late reaction was positive in 70 per cent of Mantoux (1/10) negative cases.

The results of the early and late reactions to the tubercular antigens used were similar to those of the Mantoux test in animals and human subjects infected with or sensitized to the Mantoux test. In normal subjects the results differed in more than 50 per cent of the cases.

The early reaction provoked by the tubercular antigens used is considered to be a sensitization reaction, similar to the tuberculin and Fernandez reactions. The late reactions, similar to the Mitsuda reactions, cannot, however, be considered as a prognosis reaction without further studies.

There are two papers on the *Treatment of Lepra Reaction with BCG*, by L. A. Pitt, and C. A. Consigli, and by A. J. Vaccaro, F. V. Compá and E. A. Carbani. In the latter trial 23 patients were given 200 mgm. of BCG orally once a week for 15 weeks to 8 months. The results were that in 26.1 per cent the results were good, in 17.40 per cent they were medium, and in 56.50 per cent they were nil.

In the former trial 10 patients with lepra reaction were given 200 mgm. orally once a week for 3 to 24 months. There was a marked desensitizing action in most of them with flattening of lesions, fall of temperature and general improvement of condition.

Two further papers deal with the *Mechanism of Lepra Reaction* and *Experimental Lepra Reaction*. Dr. Schujman writes of the very rare occasions in which tuberculoid leprosy is transformed into the lepromatous type.

F. F. Wilkinson and C. V. Colombo give their *New Experience with Hialuronidase Intraneurally in Leprosy*. This substance, otherwise called Diamox, was injected into 110 nerves of 64 patients suffering from painful neuritis. Half to one tablet was dissolved and injected daily for a number of weeks, the only inconvenience being polyuria. In 12 the result was excellent, in 12 it was very good, in 18 less good, in 12 slight, and in 10 there was no effect. [For another trial see the April 1956 number of *Leprosy Review*, p. 61.] F. F. Wilkinson and C. M. Brusco, writing on the same drug, question its effect on neuritis as being due only to its action as a diuretic; they think its action is more likely to be its power to regulate electrolytic balance.

Three further papers deal with legal matters concerning marriage of patients and their return home after discharge. The last three contributions describe special cases and difficulties in diagnosis.

The Argentine leprologists are to be warmly congratulated on their new venture, and on the quality of their journal.

NEWS OF BCG

Leprosy Control

[Quoted from the Chronicle of The WHO, July 1956.]

The Assembly (of WHO) considered a recommendation by the Executive Board, arising from a decision of the Fifth World Health Assembly, concerning the intensification of leprosy control and a proposal by the Government of Burma for convening a conference on this subject in South-East Asia. The Burmese proposal was strongly supported.

In India, leprosy affects 2-4 per cent of the population in regions where it is endemic and a total of approximately 1,500,000 inhabitants throughout the country. There are at least 30,000 sufferers from leprosy in Viet Nam, and so far compulsory isolation has been a complete failure, since the number seems to be increasing rather than decreasing. In the Belgian Congo, there are nearly 250,000 persons with the disease, out of a population of about 12,000,000.

Leprosy is a problem which is encountered in all the WHO regions, although in various degrees of seriousness, and the Assembly requested the Director-General to study the feasibility of holding an inter-regional conference to discuss the control of this disease in countries having similar epidemiological, social and administrative problems.

Although it is perhaps premature to talk of eradication, there is no doubt that the new methods of treatment will bring about a definite decrease in the endemicity. The various delegations which took part in the discussion of this question attached great importance to early case-finding; the selective and voluntary isolation of lepers in hospitals; mass chemotherapy, which has been found, wherever it has been employed (e.g., in India and central Africa) of value not only from the curative but also from the preventive viewpoint (mass treatment with sulfones and DDS has led to a considerable decrease in contagiousness); and the physical, physiological, functional, and occupational rehabilitation of persons diagnosed and treated in time.

Planning and Assessment of BCG Campaigns

[Quoted from Official Records of WHO, No. 73.]

The Committee considered the document entitled "Planning and Assessment of BCG Projects" and had before it also reports on the work of assessment teams in the South-East Asia, Eastern Mediterranean and Western Pacific Regions. Certain practical problems connected with mass campaigns were discussed,

particularly that of selecting persons for vaccination in areas with a high prevalence of non-specific sensitivity to tuberculin, and the question of the relatively low degree of post-vaccination allergy obtained in many areas by mass campaign vaccination, as opposed to that which had been obtained following vaccination by the assessment teams. The Committee heard that several factors, including the relative potency of vaccines, might explain these findings, but the result of the assessment work pointed especially to defects in mass campaign techniques, particularly with respect to the handling of vaccine. The Committee agreed that it was important to achieve and maintain a high standard of techniques in the mass campaigns, and that it was necessary to continue the work of the special teams for planning such campaigns and for assessing the quality of their execution.

The question of the protection against tuberculosis given to children by mass BCG vaccination campaigns in under-developed countries was discussed at the request of the UNICEF Executive Board. Controlled investigations in countries with a relatively high standard of living continue to show that BCG vaccination confers protection against tuberculosis. The Committee discussed to what extent results obtained in relatively highly developed communities might be applicable in areas where individuals had a low resistance to disease and were highly exposed to infection. The Committee agreed that there was no evidence to show that BCG vaccination could not give a similar degree of protection in such areas. The difficulties connected with carrying out scientifically controlled studies on the protective value of BCG vaccination were stressed, and the Committee on the whole felt that it did not seem expedient for such studies to be undertaken at the present time in under-developed areas, but as evidence is accumulated it should be made available.

The Committee agreed that the existing WHO/UNICEF policy on BCG mass vaccination campaigns was sound, and that it should be continued.

Effect of Storage at 37° C. on Immunizing Power of Dried BCG Vaccine, by C. Cho, *et al*, Research Institute, Japan Anti-Tuberculosis Association, Tokyo, Japan.

[The following is the synopsis from the Bulletin of WHO.]

Experiments were carried out to determine the effects of storage at 37° C. on the immunizing power of dried BCG vaccine. Vaccines were prepared with sodium glutamate and with sucrose, and were preserved for 6 months at 5° C. and at 37° C. The pre-

served vaccines were then injected into four groups of 12 tuberculin-negative guinea-pigs; a fifth group of 12 non-vaccinated animals acted as controls. Six weeks after inoculation, all surviving animals were given a challenge dose of virulent human tubercle bacilli. After a further six weeks the guinea-pigs were killed and an examination was made of the macroscopic and histological changes produced in the lymph-nodes and viscera.

No significant difference in the tuberculous changes induced by the challenge infection was observed among three of the groups of vaccinated animals—namely, the two inoculated with the sodium glutamate vaccines and the one inoculated with the sucrose vaccine preserved at 5° C. The fourth vaccinated group showed greater changes than the other three, indicating that the immunizing power of the sucrose vaccine had decreased markedly during storage for 6 months at 37° C. The non-vaccinated control group, however, showed the most conspicuous changes of all the five groups.

BCG Vaccination in Lepromatous Leprosy

[The following is abstracted from a paper by Dr. J. A. Doull, of the Leonard Wood Memorial.]

At present, with the co-operation of Philippine and South African institutions, the Memorial is conducting a controlled study of the effect of repeated BCG vaccination in patients suffering from lepromatous leprosy who were negative to tuberculin and to lepromin at the outset. The vaccinated groups are carefully matched against other groups comparable as regards age, sex, stage of disease and other factors. This study will be carried on at each of three institutions for 48 weeks. Judging from the experience of others it seems probable that some will become reactive. Whether or not this reactivity will be postively associated with clinical or bacteriologic improvement is a question which can be answered only when the final condition of the group receiving BCG is compared with that of the other groups.

British BCG

[Quoted from the Lancet, June 30th, 1956.]

The rather tentative official support for BCG in this country in the past few years has been fortified by a statistically unassailable experiment; and, although the vaccine cannot yet be freely used, there are signs that control is being relaxed. So far all the BCG vaccine routinely used in this country has been imported. But the first report of a British BCG, a freeze-dried vaccine, has now appeared. Freeze-dried vaccine, if it is as con-

sistently potent as the liquid products, has obvious advantages. It can be kept for many months at room-temperature without serious loss of potency, so that each batch can be fully tested before it is released. Instead of having to be ordered in advance and used without a delay, the freeze-dried product can be kept in store and is promptly available—an obvious advantage to those who use it infrequently and in small quantities. Freeze-dried vaccines have been manufactured and tested in many countries, notably in France, the United States, Russia and Japan. The extensive Japanese experience of its manufacture has recently been reviewed by Obayashi in a WHO monograph.

The new British vaccine was produced in the Glaxo laboratories and, after detailed bacteriological and animal tests, two batches were put to clinical trial. Lorber and his colleagues vaccinated 276 newborn infants. After six weeks 88% of those vaccinated with one batch and 77% of those vaccinated with the other gave a positive tuberculin skin reaction. But twelve weeks after vaccination the proportions of " convertors " has risen to 96% and 92%. This delay in the appearance of the sensitivity produced by freeze-dried vaccine was also noted by Ebina *et al.* The vaccination lesions were small and in only 8 infants were there palpably enlarged axillary lymph-nodes. None had any detectable general disturbance of health. The vaccine was kept at room-temperature during the fourteen weeks of the trial. There was no important change in the vaccine during this period and counts of viable cells were of the same order as at the start of the investigation. Lorber *et al.* believe that this particular British freeze-dried vaccine would not be suitable for vaccination of contacts; for it may be desirable in contacts to induce tuberculin skin sensitivity as quickly as possible with the least risk of failure. This is, however, not a serious deficiency; for most of the vaccine required in this country will probably be needed for routine vaccination of those not especially exposed to infection.

REPORTS

Ceylon

The following statistics are quoted from the Administration Report of the Director of Health Services for 1955.

316 new cases have been detected during the year as against 265 last year.

Incidence by Age Groups, Type and Sex

	Lepromatous		*Neural*	
Age Groups	*Male*	*Female*	*Male*	*Female*
0— 4	—	1	1	3
5— 9	1	—	9	6
10—14	3	2	9	2
15—19	6	1	8	4
20—29	26	6	33	15
30—39	19	2	28	10
40—49	15	2	24	12
50—59	15	1	20	7
60—69	5	3	4	3
70— +	2	1	6	1
Total ...	92	19	142	63
Type ...	111		205	
	Male		*Female*	
Sex ...	234		82	

British Guiana

REPORT ON LEPROSY FOR 1953

The number of known cases of leprosy in this Colony at the end of the year was 1,213 which shows an incidence of 2.7 per 1,000 of the population. Of this number, 233 cases were treated as in-patients and the remaining cases as out-patients. As in previous years, School Surveys were conducted by a specially trained Health Visitor and 25 cases of early tuberculoid leprosy were detected among 48,152 children examined. The prognosis of cases found at School Surveys was good when attendance at clinic was regular.

East African Leprosy Research Centre

The East African Council for Medical Research in their 1954-55 Report states:

The idea for the Research Centre originated in the British Empire Leprosy Relief Association, who had earlier founded a similar Research Centre in Nigeria, later handed over to government, in which the late John Lowe did the work which helped to establish the drug DDS as a cheap and efficient treatment for leprosy, which drug has now become a standard throughout the world. The greater part of the finance for the East African Centre was provided by BELRA, and the East African Governments have

contributed, as BELRA, to both capital cost and maintenance, and the new unit is administered by the E.A.H.C., seeing that it is an institution designed to benefit all the territories.

It is expected that 1956 will see the development of full work at the East African Leprosy Research Centre. It is proposed, because of the existence of a memorial fund to the late John Lowe being built up by the City of Birmingham, he being a distinguished son of that city, to designate these laboratories the " John Lowe Memorial Laboratories ", the proceeds of that fund being used to defray the original cost and, it is hoped, much of the future cost of this work.

Dr. James Ross Innes, who for many years was Inter-territorial Leprologist for East Africa, and later became Director of the Leprosy Research Centre, is retiring from the latter post to become Medical Secretary of BELRA in place of the late Dr. John Lowe. He will be succeeded as Director of the Research Centre by Dr. John Garrod, until recently leprosy specialist for N. Rhodesia.

Leprosy Control in Madras

[Extract from Hindu, Madras, September 12th, 1956.]

Two things emerge with heartening clarity from the reports of the anniversary celebrations of the Madras State branch of the Hind Kusht Nivaran Sangh and the Press Conference held in that connection. One is the increasing measure of success achieved in the treatment of leprosy by the use of sulphone drugs which have worked somewhat slow but steady and certain cures and have, in the words of the State Public Health Minister, " brought a new outlook on leprosy control by giving the hope both to the patient and the community that they can get rid of leprosy ". Already 96 Government medical officers have been trained in the use of sulphones and more are to be trained. It is also good to know that these drugs are available in every Government dispensary. Both official and non-official agencies must pool their resources and their services and enable every sufferer to get the benefit of this treatment. Some idea of what can be achieved in this direction is given by the figures relating to the Leprosy Institute at Tirumani. There the number of patients discharged after the disease had been arrested rose from 66 in 1950 to 243 in 1955. It was too early to say if the disease was on the decline. It had perhaps increased only in relation to the proportion of the population. They might say that it was merely static.

Mr. Shetty said that the Government of India had under consideration a proposal for trying BCG as a prophylactic in some of the leprosy research centres, for the purpose of investigations.

ABSTRACTS

Lupus Vulgaris

[In view of the resemblances between lupus vulgaris and leprosy, particularly the tuberculoid type, the following summary from the *Lancet* (Oct. 20th, 1956, p. 813) of results of treatment with isoniazid are of interest.]

Results obtained with isoniazid in 111 cases of lupus vulgaris are reported after four years' experience with the drug.

Improvement took place in all the 103 patients who completed the course of treatment, and in 99 of them the lesions were clinically cleared. In 3 of the others they have since cleared with other treatment, while the 4th has refused local treatments.

The 99 patients whose lesions cleared have been followed up for six to twenty-four months after the completion of their courses. Relapses (with solitary or grouped nodules) have occurred in 11, in whom the average length of treatment was thirty-two weeks and the average total dosage of isoniazid was 79.5 g. In the 88 patients who have not relapsed, the average length of treatment was forty-six weeks and the average total dosage was 108.5 g. Nine of the relapsed cases have cleared again with various treatments and 2 are improving on a second course of isoniazid.

For adults, it is advisable to give isoniazid in a dose of 300 mg. a day for a period extending up to at least three months after clinical clearance. This usually entails treatment for a year with a total dosage of about 110 g. but in selected cases a total of 150 g. may be thought necessary. A daily dose of 400 mg. has not brought about earlier clinical clearance.

The incidence of new cases of lupus vulgaris at the London Hospital has fallen remarkably in the last few decades. This is attributable to cleaner milk, earlier recognition and improved treatment of pulmonary tuberculosis, and better nutrition and housing.

Kaoru Urabe, *et al.*, write on *Studies on the in vivo Cultivation of Murine Leprosy Bacilli* in *La Lepro* (Jan. 1956).

The following is an abstract:—

Cultivation of murine leprosy bacilli in vitro has not proven entirely satisfactory. Studies were conducted on *in vivo* cultivation as an indirect aid to clarifying the mode of propagation of the bacilli. In order to avoid the partial observations resulting from *in vivo* methods used heretofore, phase contrast microscopy and the slide culture method *in vivo* were utilized. The following results were obtained.

(1) Murine leprosy bacilli show elongation, branching and granules formation similar to growth of other acid-fast bacilli on the slide inserted under the skin of the white rat.

(2) It is suggested that murine leprosy bacilli will multiply even in the absence of body cells if there is adequate infusion of body fluid in a susceptible animal (white rat) under conditions where invasion of body cells is obstructed.

(3) Propagation of murine leprosy bacilli in murine leprosy-sensitized white rats is slow and minute compared to the non-sensitized control.

***Trop. Dis. Bull., Vol. 53, No. 10, October 1956**

Outlines of Campaigns against Social Diseases. IV. The Recently Passed Italian Legislation for those suffering from Leprosy, whether Arrested or not, with a Brief Indication of the Statistical and Epidemiological Situation of Leprosy in Italy, by **G. Del Vecchio.** Igiene e San. Pubblica, Rome, 1956, Jan.-Feb., Vol. 12, Nos. 1/2, 50-63. [13 refs.] English summary (8 lines.)

At the end of 1955 there were in Italy 443 patients known to be suffering from leprosy, of which 193 were interned in hospitals and 250 at home. There were also records of 213 such patients who had died in recent times. The largest concentration (102) was in Calabria, the second largest (80) in Sicily, and the third (50) in Apulia. Laws which have been recently promulgated provide for more accommodation for leprosy patients, especially in rural colonies, and make provision for relatives and other dependents of patients. In 1947 Tobia claimed that there were 364 with leprosy in Italy, of whom 84 had entered from outside, 175 had acquired the disease in the country, while in 105 the origin of the disease was uncertain. In 1954 Manca Pastorino assessed the number of leprosy patients at 400, and in the end of that year the number was found to be 434. The measures adopted in other countries for the control and relief of leprosy are quoted, and on the results obtained in these countries the present new regulations are based.

Leprosy: A Changing Situation in Eastern Nigeria, by **T. F. Davey, C. M. Ross** and **B. Nicholson.** Brit. Med. J., 1956, July 14, 65-8.

Up to 1948 the incidence of leprosy in Eastern Nigeria was phenomenally high; for instance a survey of the Abua clan in 1937

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showed 492 patients with active leprosy in a population of 14,515 (34 per thousand). The character of the disease was, however, mild, lepromatous cases forming a small minority, and indeterminate cases being common.

Since 1948 a steady reduction has gradually become evident. Typical of this, in one group of villages where work began in 1941 the new cases in the first three years were 37, 45 and 71, while in 1952, 1953 and 1954 there were only 8, 10 and 8 respectively. It was possible to maintain a close watch for new cases, but patients co-operated and " came forward for treatment on their own initiative, presenting extremely early lesions ". The question is asked: has there been an epidemic with a rapid decline over a short period of years? This might have resulted from the sudden opening up of the country under British rule without corresponding sanitary safeguards; the people themselves are of the opinion that leprosy spread rapidly during that period. Leprosy is common among both chidren and adults, " and the unstable indeterminate and borderline varieties of leprosy among the higher age groups is particularly suggestive. It is what one would expect in the earlier stages of an epidemic with all age groups susceptible."

There is also the possible effect of cross immunity with tuberculosis, but " the impression remains that, even if tuberculosis is having a limiting effect on leprosy in and around ports and townships, its effects in remoter rural areas are not yet sufficient to have contributed much to the decline of leprosy already observed in such areas ".

Another factor to be considered is the improvement in sanitation, standard of living, child health and medical facilities. Then there are the leprosy control measures which were begun about 1935; many local anti-leprosy schemes spread throughout the area from 1938 to 1943, in which entire communities often participated. Over the last 20 years several thousands of those with the lepromatous type were isolated in settlements in E. Nigeria, and " in Owerri and Rivers Provinces, during the past 15 years approximately 10,000 patients have been isolated for longer or shorter periods in local segregation villages ".

Lastly, there is the effect of sulphone treatment. Since 1949 treatment with oral DDS has gradually been introduced. " Treatment is extremely popular, attracting patients at an earlier stage of the disease than ever before. Early lepromatous cases speedily become baceriologically negative. The general public is increasingly leprosy-conscious, and prejudice in localities long resistant to local leprosy control measures has finally succumbed.

Relapses hitherto have been unimportant, and there have been no grounds for losing the confident outlook that sulphone treatment engendered."

While natural regression, the spread of tuberculosis, and the higher standard of living have a part, there is no doubt that the intense and widespread leprosy control work has been of extreme importance, and that its cost to the British taxpayer has entirely justified itself.

Leprosy and Childhood, by **J. A. K. Brown.** Central African Journal of Medicine, 1956, May, Vol. 2, No. 5, 173-80.

From his experience of leprosy in Uganda and Nigeria the author questions the conclusion that leprosy has any predilection for children. In Southern Nigeria one third of the patients in settlements were under 15; in the Uganda leprosarium at present 29 per cent are children. " In one of the larger leprosaria [in Uganda] at a recent examination, 225 (36 per cent) of 631 resident patients had been admitted during childhood, but in this particular district children form about half the population." It is an error to think that susceptibility diminishes with age. " It may be distressing to know that 27 per cent of the leper population of East Africa is under the age of 20, but it is important to remember that the other 73 per cent got through their childhood and adolescence safely, only to become infected after reaching maturity." [It is difficult to say how many of the 73 per cent were infected, though without showing symptoms, before the age of 20. A low child rate is often regarded as a sign that the epidemic is on the downgrade.] The suggestion is made that the more susceptible children are usually those ' one of whose parents had leprosy. Where both parents have the disease the susceptibility is presumably greater still." [This assumes hereditary susceptibility, but no evidence in favour of this assumption is put forward.]

The Differentiation of Hansen's and Koch's Bacilli by Staining with Sudan Black, by **F. Contreras, J. Guillen** and **J. Terencio.** Rev. " Fontilles ", Valencia, 1956, Jan., Vol. 4, No. 1, 15-16.

A half per cent solution in absolute alcohol of Sudan Black B is incubated at room temperature for 48 hours; 7 cc. of this is mixed with 3 cc. of distilled water, shaken and filtered twice. A 1 per cent aqueous solution of safranin is used as the differential stain. The Sudan Black is decolourized with acetone. With 51 smears from nose and skin of lepromatous patients all were positive using the usual Ziehl stain; but all were negative with

Sudan Black, though when restained with Ziehl they all became positive. All of 10 smears from positive tubercular sputum were found positive with both Ziehl and Sudan Black. It is considered that the use of Sudan Black is a useful differential method for distinguishing between tuberculosis and leprosy.

Clinical and Immunological Results in Adult Leprosy Patients Vaccinated Orally with BCG, by **F. Contreras, J. Guillen, J. Tarabini** and **J. Terencio.** Rev. " Fontilles ", Valencia, 1956, Jan., Vol. 4, No. 1, 33-8.

Sixteen lepromin-negative leprosy patients (15 of them of the lepromatous type) were vaccinated orally with BCG. The amount given was approximately 0.1 gm. once a week for 3 weeks, only one patient being given 0.2 gm. In none of the patients was there a change in the lepromin reaction to positive. In a group of 11 of these patients who were suffering from lepra reaction the reaction disappeared permanently except in two, in whom it became slight and fugitive. With the exception of one patient who belonged to the dimorphous group, all the patients improved in general health and wellbeing. While this improvement may be due in part to other forms of treatment, it was considered that in some cases the improvement was caused by the vaccination with BCG.

Combined Use of INH and DDS in the Treatment of Leprosy, by **Dharmendra and K. R. Chatterji.** Leprosy in India, 1956, Vol. 28, No. 1, 3-6.

In a previous article the authors reported that INH was of definite value in the first 8 to 12 weeks of treatment, but that after that there was a setback. They suggested its use in combination with sulphones. In this trial 24 patients of the lepromatous type were at first taken, but 2 were not included in the results because treatment was too short. The remaining 22 were treated from 20 to 103 weeks. The dose of INH was 50 mgm. quickly increased to 200 mgm. daily. That of DDS was 25 mgm. slowly raised to 10 mgm. daily. Toxic signs were practically nil, and at least less than with DDS alone. Of the 22 patients 6 showed marked improvement clinically and bacteriologically, 9 showed moderate improvement, and 7 slight improvement. " The combined treatment with INH and DDS appears to be more effective than with either of the drugs alone. It is possible that the addition of DDS delays the development of INH resistant strains of the leprosy bacillus."

Isoniazide in High Doses along with Streptomycin and Aminoacids in the Treatment of Leprosy, by **G. Tarabini Castellani.** Rev. "Fontilles", Valencia, 1956, Jan., Vol. 4, No. 1, 19-31.

Two series of patients were treated: the first (of 8 patients) with isoniazid and streptomycin with the occasional addition of glutamin acid; the second series of 3 patients with isoniazid and glutamin acid throughout. Details of each patient are given. Glutamin acid was given for its detoxicating effects. Of 7 severe lepromatous cases 3 became permanently bacteriologically negative in the nasal mucosa, but only one become temporarily negative in skin examinations. One patient improved only very slightly, probably due to acquired resistance to INH. Two patients with many bacilli treated with the glutamic acid combination showed temporary improvement, but relapsed again within 60 days. It is considered that while generally speaking the best treatment is with sulphones, there are certain cases which will initially improve better on a combination of INH and streptomycin; but the improvement is only transitory unless it is followed up by sulphone treatment. The maximum daily dose of INH varied from 1,200 to 2,000 mgm.

***Trop. Dis. Bulletin, Vol. 53, No. 11, November 1956**

A Note on the Less Familiar Forms of Leprosy, by **H. W. Wade.** Leprosy in India, 1956, April, Vol. 28, No. 2, 41-9. [30 refs.]

It is emphasised that the primary criterion of classification is clinical, the Mitsuda test and histopathology being contributary but secondary. The intermediate group is counted as those with simple flat macular lesions in the course of development. Some of these will become lepromatous, others tuberculoid. Those which take neither of these two courses but remain pale and anaesthetic should be classified as maculo-anaesthetic, whether or not they are accompanied by clinical affection of the related nerves.

Major and minor tuberculoid forms are both chronic, and the former should not be regarded as a reacting form of the latter. Two kinds of reaction are described in the tuberculoid type: *tuberculoid reactivation* where the nature of the lesions does not change in spite of the acute condition, and reactional *tuberculoid leprosy* with a relatively abrupt onset that causes marked clinical and histological changes. The border-line form occurs in a tuberculoid where there is loss of resistance for some reason or other, chiefly as the result of repeated reactions; but it is not in itself reactional. These cases are liable to be mistaken for lepro-

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matous, and the Mitsuda reaction may be negative; there are likely to be abundant bacilli, but the histological picture is different from that of the lepromatous type. They retain potentially some degree of resistance, but if left to themselves tend to become lepromatous. The question arises as to prognosis in cases which were formerly borderline and still retain that potential resistance.

Two kinds of lepromatous reaction are described: the ordinary acute reactivation where there are many bacilli, and the acute infiltration (pseudoexacerbation) in which there are fewer bacilli. This latter occurs in patients under sulphone treatment, and it has been suggested that it occurs in those who had previously suffered from the borderline form but had gone on in the direction of lepromatous, and that this reaction is a sign of this process in reverse and an attempt to change latent into active resistance.

Lastly is mentioned the " spectrum " concept, that while polar cases are most common, there are between the two poles various gradations, and " intermingling and blending of the features of related varieties ".

[This paper is one of considerable value, and should help to clear up various points in classification which are difficult to understand.]

In the **Archives of Leprosy,** Minas Gerais, Brazil, Oct. 1955, Dr. Diniz reports in his summary:—

The author, who for the last years has done prophylactic work against leprosy, gives a broad sketch of the situation of that disease in the State of Minas Gerais. He states that the number of patients has steadily increased from 2.25 per thousand inhabitants in 1950 to 2.71 in 1955. The index of prevalence has risen from 1.38 in 1944 to 1.95 in 1954. He also states that the infectious forms of the disease showed a percentage of 66.55, being thus higher than the percentage for the rest of the country, which is 56.5 per cent. He then alludes to the prophylactic measures adopted in the State where there are six leper asylums, housing 5,518 patients.

" In spite of the worsening situation, the author recognises the benefit of isolation as practised intensively for more than 20 years, for without it the situation would be still worse. He proposes the adoption of a new method of combating the disease, a method which he has advocated on several occasions. The specialists in leprosy, whose number is small, could work in conjunction with the specialists in medical sanitation, who in their

territory could take an appreciable part in the campaign in the following ways: education of the masses, education of communicants, sulphonic treatment, selective isolation."

On page 257 of the above Journal, Dr. José Mariano reports the use of Sulfon Cilag, which he injects intradermally into lesions using a 10 per cent solution in distilled water, and injecting as much as 5 cc.s at one sitting. This was repeated every eight days and was found to help in clearing up resistant lesions.

On Leprosy in Martinique, by **E. Montestruc.** Biol. Med. 1956, May-June, Vol. 45, No. 3, 247-343, 2 figs.

Leprosy was unknown in this Caribbean island till its first mention in 1751. From then on the history is traced. A systematic survey was not made till 1933. For a time patients were lodged in a leprosarium at Desirade. But this place was not at all popular and was an obstacle to gathering patients for treatment. In 1948, when Martinique, Guadeloupe and Guiana became departments of France, a more liberal policy was adopted and pavilions attached to the hospital at Fort-de-France were erected, sufficient to hold 120 patients. During the years 1934 to 1954 the annual numbers of patients registered rose from 66 to 196, making a total for these 21 years of 1,648. From 1948 to 1954 the 821 patients registered were classified as 28.3 per cent lepromatous, 15.9 per cent tuberculoid, and 55.7 per cent indeterminate. As to ages, during the longer period of 21 years, 29 per cent were under 15, and 53.1 were less than 25 when registered. As regards familial infection, out of the last hundred patients registered 51 were brothers and sisters, 18 had maternal infection and 14 paternal, 9 were avuncular, 7 were cousins, and there was 1 conjugal. It is calculated that in 1954 as many as 700 to 800 patients received ambulatory treatment in dispensaries or from private doctors. About 150 were treated in the special hospital wards. Unfortunately these beds instead of being used for short periods for patients needing temporary treatment, 50 per cent are blocked with incurables. In spite of sulphone treatment, the disease seems to be increasing rather than diminishing, largely due to patients taking treatment irregularly. This is shown by the fact that in 1954, 196 new patients were registered, of whom 45 were lepromatous, 13 tuberculoid and 122 indeterminate, a total number 3 times that of 20 years ago. The article compares the leprosy epidemic to that of poliomyelitis, only that the latter is receiving abundant attention, while leprosy is being comparatively neglected. It finishes with a programme considered indispensable for the elimination of leprosy in the years to come.

The Classification of Leprosy (an Historical Survey of the Problem with Comments on the Recent System proposed at Madrid), by **H. v. R. Mostert.**

This is a clearly written and well-illustrated article, particularly suitable for helping the general medical practitioner to recognise the abstruce divisions and subdivisions under which leprosy is classified. The historical survey traces the various nomenclatures which have been used from the time of Hansen up to the Madrid Congress in 1953. Though classification is primarily clinical, a certain amount of laboratory help is needed. Fortunately for those in outlying areas in Africa most cases are either tuberculoid or lepromatous, presenting typical lesions clinically.

Drs. Francisco Compa and **Jose Fernandez** write on *BCG in the Prophylaxis of Leprosy*. Revista Argentina de Dermatosifilogia, Vol. 39, 1955.

The course of the disease is described in a girl and a boy who had lived with their lepromatous mother till they were respectively 4 years and 18 months of age, when they were removed to a preventorium. The lepromin reaction of both was at that time negative. To convert the reaction to positive they were given 9 intradermal injections of 0.1 c.c. of bacillary lepromin, but without result. They were then given 100 mgm. of BCG orally. Two years later the girl was free from leprosy, but the boy showed tuberculoid lesions. The lepromin reaction of both had become positive. Four years after the first examination the girl was still free from leprosy, and the lesions of the boy showed regression, though he had had no treatment. The lepromin reaction of both remained positive. The authors ascribe the favourable immunological changes in the children to the vaccination with BCG.