EDITORIAL

Visit to South Africa: 1st—10th April, 1959

The Secretary for Health of the Union of South Africa kindly welcomed a visit from the Editor to see something of the leprosy work in Westfort Institution, Pretoria. It was possible to spend 10 days there, and it was a very stimulating experience, for the work under Dr. A. R. Davison, the Medical Superintendent, is of the highest quality. Westfort is an institution containing over 900 patients. Dr. Davison is assisted by Dr. Egnal, Dr. Doevendans, and Miss Kellerman, the matron, with four sisters and 15 European female nursing assistants, and Mr. Tilley and Mr. Banks for the management. There is a holiday home on the coast called the Lady Mary Baring Home. The results of the work have been good as there have been definite signs of a reduction in the intake of new cases of European and coloured patients. The average intake of all cases is about 600 per annum. There have been great increases in the number of discharges but so far no decrease in total notifications. In the whole of the Union there are four institutions with a total of 1,613 patients. The equipment, housing and buildings of Westfort are first class, and there is complete availability of all drugs and special procedures necessary for all features of leprosy morbidity. Dr. Davison kindly gave up his time to make thorough demonstrations of the patients and of his method of treating them. Research projects go on at Westfort and it has participated recently in the therapeutic evaluation projects of the Leonard Wood Memorial. It became clear, as the cases were demonstrated day after day during the visit, that the type of leprosy in this region should be placed further to the left of the spectrum of leprosy which has lepromatous on the left than the leprosy of countries like East Africa or Nigeria. There was a far greater tendency here to all forms of lepra reaction, and in particular erythema nodosum leprosum. Dr. Davison has had great success with the protection and management of patients in these reactions, and his great contribution has been the demonstration of the value of the antimalarial type of drug (mepacrine and camoquin) in conjunction with ACTH and other corticosteroids. Of particular interest were some signs of the Lucio phenomenon, and of the pellagra factor.

It became quite clear that the work of leprosy in the Union is of the highest standard and humanely carried out. It is hoped that the other sections of work in the Union may be seen on a subsequent visit.

Visit to Brazzaville for the WHO Conference for African Leprologists on Leprosy in Africa: 14th—22nd April, 1959

This congress was organised by WHO, the secretary being Dr. J. Gay Prieto, Chief of the Leprosy Section of the Division of

Communicable Diseases of WHO. It was attended by over 40 leprosy workers and the Chairman elected was Médecin-Général Richet, with Dr. Davison of South Africa as Vice-Chairman. The great value of this conference was the opportunity of so many leprosy workers in Africa getting together and getting to know each other's point of view and hearing about each other's work. There was an opportunity during the conference of seeing the work at Dolisie in French Equatorial Africa and the work at Leopoldville in the Belgian Congo, both of which were very instructive to all the visitors.

With Africa in a ferment of political changes in progress and to come, it was of great value for such a meeting to be held. Each country differs from the other considerably in local conditions and in resources with which to fight leprosy. It was impossible to lay down a hard and fast rule for the control of leprosy in Africa, and it was fascinating to see how each country had applied the principles of leprosy control with adaptability and commonsense. Apart from the more advanced countries where leprosy is well integrated into the Department of Public Health, it became evident that the control of leprosy in Africa would continue best in those countries where trouble had been taken to instruct and train nationals of that country to assist in the leprosy campaign.

Further News of Macrocyclon (See *Lep. Rev.* **29,** 2; Apr. 1958, p. 68)

Macrocyclon is one of the polyoxyethylene ethers which are surface-active agents. Dr. J. A. McFadzean has given a preliminary report, as at 12th September, 1958, to the Leprosy Sub-committee of the Colonial Medical Research Committee, London, on a trial on human leprosy. There were 6 adult males with lepromatous leprosy, balanced with 6 similar cases on DDS. All patients were given a high protein diet throughout the trial, and for a month before it. The macrocyclon patients were given weekly intravenous injections of the drug at 25 mg./kilo for 14 weeks, thereafter gradually increased to 50 mg/kilo over a period of 8 weeks. The control patients were given 400 mg. of DDS in oil weekly intramuscularly in a divided dose for 5 weeks, raised to 600 mg. weekly thereafter. Full laboratory observations were done, and included the assessment of bacterial index by biopsy (by Dr. D. S. Ridley, of the Hospital for Tropical Diseases, London). In one patient there was a fall in the B.I. of 95% but in the other cases it seemed that macrocyclon was clinically much inferior to DDS, this being supported to some extent by the biopsies. There was evidence that macrocyclon produces a mild degree of renal damage. All the patients showed a constant albuminuria which improved after cessation of the dosage. The trial was therefore brought to an end. Dr. McFadzean suggests that further trials of macrocyclon alone are not warranted, but there might be value in a

trial of it at 25 mg./kilo in combination with DDS, and compared to sulphone alone. This trial will probably be carried out by his successor, Dr. M. F. R. Waters, at Sungei Buloh Research Centre in Malaya.

The Nature of the Mitsuda Reaction

We directly requested Dr. R. Kooij to state his present lines of thought on his very interesting work on the nature of the lepromin and allied reactions, and he has responded as follows:

"In my ensuing remarks I leave aside the Fernandez reaction of the lepromin test and confine myself to the Mitsuda reaction which is read 3 or 4 weeks after the intradermal injection of lepromin. I have shown that not only the leprosy bacilli are responsible for the evoking of the Mitsuda reaction, but that also the tissue component plays a role and that even with normal tissue suspensions without bacilli, positive reactions of Mitsuda type are obtained in tuberculoid leprosy, and negative ones in lepromatous leprosy. This explains why the lepromin reaction is not a specific reaction for leprosy and fails to be of diagnostic use. It is of use for the classification of leprosy. The typical feature of the Mitsuda reaction is not its positivity in the tuberculoid leprosy, but its negativity in the lepromatous type. Most adult healthy people show a positive Mitsuda reaction to standard lepromin.

The negative Mitsuda reaction in the lepromatous type is probably due to the inability of patients of that type to break down the leprosy bacilli. This perhaps may be the fault of the reticuloendothelial system, expressed as a lack of special enzyme systems in individual constitutions. The lack of reactivity to lepromin among infants and the gradually developing response among growing children may be interpreted as a manifestation of a normal maturation cycle. Contact with leprosy bacilli is not necessary for this reactivity to lepromin (Kooij and Rutgers, Internat. J. of Leprosy, **26,** 24, 1958; Swerts, Ann. Soc. Belge Med. Trop. **35,** 801, 1955). However, Kooij and Rutgers showed that the reaction to lepromin was accelerated and intensified by leprosy and tuberculosis. Probably these facts might give an explanation of the conversion of negative lepromin reactions to positive by BCG vaccination, perhaps owing to the non-specific Dienes effect, although cross sensitization cannot be ruled out with certainty.

The possible protective influence of BCG vaccination against leprosy could also be explained by the non-specific Dienes effect. The Mitsuda reaction is an unusual type of reaction. There is only one similar reaction in clinical use. This is the Kveim reaction in sarcoidosis. We also found that similar reactions could be obtained with normal tissue suspensions.

The above three reactions have many things in common; they

have the same method of preparation, evoke the same histological picture, and the active principle is bound to the particulate matter.

Probably we are dealing with a kind of foreign body reaction or isomorphic (isopathic) phenomenon of certain individuals due to their individual constitution. With the above three reactions we can detect this mode of response in individual constitutions.

More knowledge about the nature of these reactions may lead to a better understanding of the pathogenesis of leprosy and sarcoidosis. Not much is known about the nature of these so-called foreign-body reactions; they are not easily evoked, very special conditions being required. Several attempts in the past have been made with normal tissue to evoke a positive Mitsuda reaction in patients with tuberculoid leprosy, but without success until my recent work. Furthermore, many experiments have been carried out with normal tissue suspensions to evoke a positive Kveim reaction in patients with sarcoidosis (by Danbolt, among others), usually with negative results. The reason for this is that probably the preparations were not concentrated enough and did not contain sufficient particles of a certain size and chemical composition. Attempts at evoking positive reactions in patients with sarcoidosis by injecting particulate and other elements into the skin, e.g., catgut (Danbolt), silicate (Refvem), talc and aleuronate (Hathausen), Indian ink and paraffin oil (Schauman and Seeberg) have given negative results.

It seems that very special conditions are required for evoking the Mitsuda type or Kveim type of reaction.

It is of the utmost importance to obtain more knowledge of these conditions for the understanding of leprosy and sarcoidosis. Although in the disease leprosy the leprosy bacillus is essential to the occurrence of the disease, it is not the only factor. The severity of the infection, or even whether or not the disease will become manifest, is chiefly determined by other factors, particularly by the mode of reaction due to the individual constitution. In leprosy we should begin to introduce the polyvalent concept into our thinking about the cause of the disease and to study the constitutional aspects of it more intensively.

Leprosy can evoke pictures indistinguishable from sarcoidosis. The study of the pathogenesis of the *syndrome* sarcoidosis (including silicosis) might be of value for a better understanding of leprosy and *vice versa.* The study of the conditions and nature of the Mitsuda reaction, the Kveim reaction, and the reaction to normal tissue suspensions might be very helpful in this respect; most value will lie in further studies of the required conditions of the reaction to suspensions of normal tissue."

We also asked certain workers for comments and so far the following has come from Dr. F. Sagher, of Jerusalem:

"*On the nature of the isomorphic and isopathic reactions in*

leprosy. As far as we know only leprosy and sarcoidosis react to injection of materials taken from patients with these diseases with a reaction after 3-5 weeks. This reaction is histologically of the same nature as the original disease process and therefore it can be called an isomorphic or Koebner's phenomenon. The difference from the original Koebner's phenomenon, as typical in psoriasis and lichen planus, is only that in the first two diseases the histological reaction is a granulomatous one whereas in both latter diseases a great part of the changes is found in the epidermis. In contrast to the isomorphic phenomenon is the isopathic phenomenon[1, 2, 3, 4] which is a reaction caused by living organisms and is producing a granuloma similar to leproma and not to a tubercle after injection of BCG or leishmania after injection of flagellates of *Leishmania tropica*.

These facts have been worked out mainly in lepromatous and in arrested cases but not enough experience has been gathered in the tuberculoid or indeterminate form.

This leproma-like reaction could be elicited also by leishmanin, tuberculin, milk, or peptone injection or sand-fly bites and Richter[5] was able to elicit reaction after injection of Indian ink. The occurrence of the isopathic changes was found by him also in an indeterminate case and he suggests a possible diagnostic importance in bacillus-poor cases.

Also Waaler[6] from Bergen could find an isopathic response in two patients, one of them with active leprosy and one with residual, and a non-characteristic reaction in further two residual or subsidial patients. He also made an attempt to induce isopathic reaction in his own skin by adding a suspension of skin from one of the leprosy patients to tuberculin, but a passive transfer of the isopathic ability did not occur.

Very thorough speculations concerning these facts were pointed out by Wade in an Editorial of the International Journal of Leprosy[7]. It appears from this observation that in lepromatous leprosy (tuberculoid and indeterminate cases have not been studied in a sufficient number) there is a profound specific alteration of the tissue reactivity of the host which causes various substances to elicit changes characteristic of the disease process irrespective of bacilli at the sites. This alteration may persist long after a case is bacteriologically negative. There is no relation to the patient's reactivity to tuberculin or lepromin and the nature of the injected material seems to be of little consequence.

It is interesting to note that also in sarcoidosis some authors have claimed sarcoid reactions after the injection of tissue from normal spleen but others have not found a reactivity to material other than from sarcoid lesions.

The isopathic reaction can be used to find out whether the skin of a contact of leprosy is already reactive with a lepromatous or

prelepromatous reaction, and this could give some hint whether such a contact will develop the disease or not. But this problem is certainly a long term one and difficult to prove. The reactions seems not to subside by the arrest of the disease following treatment over many years.

Kooij[8] pointed out that the leprosy bacillus although essential for the occurrence of leprosy is not the only factor determining the occurrence and development of the disease and this experimental observation may speak in favour of his opinion.

With all the knowledge today accumulated by the various experiments only some of the problems have been touched but much remains to be learned before we shall have a complete explanation of all these humoral responses."

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This subject remains open for discussion, and contributions are welcome. See abstract of another article by KOOIJ in Dermatologica, **117**, 5, 1958, which is given in this issue of *Leprosy Review*, p. 198.