LEPROSY REVIEW

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EDITORIAL

Visit to Ghana

The Editor again has had the privilege of a visit to one of the countries where active and extensive leprosy control has been in progress. We received the invitation of the Hon. The Minister of Health, Ghana, and arrived in Accra on 16th April, 1958, and left again for London on 30th April. Dr. A. McKelvie the specialist leprologist in charge of the Ghana Leprosy Service met us at the airport and personally accompanied us throughout a very strenuous but eminently satisfactory tour of much of the leprosy work in Ghana, and extraordinary kindness and assistance was given by everybody in the Ministry and throughout the tour. It is twelve years since the Medical Secretary of BELRA visited Ghana. At that time it was Dr. Ernest Muir, who had previously visited the country in 1936, and whose wise advice has been the basis for the attack on leprosy which is going so strongly today.

Sparing the reader the details of the missions, hospitals, and clinics visited; it will suffice to say that by hard work and much travel, an extremely full contact was obtained with the leprosy work in progress, and above all it was possible to see a very large number of leprosy patients under treatment and the staff who are actively engaged. The competence and good spirit of the staff were everywhere apparent. Ghana contains a population of over 5,000,000, rather unevenly distributed, and leprosy surveys indicated an incidence of 50,000 cases of leprosy. Dr. McKelvie devised a plan to suit the conditions of the country, whereby the essential and basic leprosaria were supplemented by mobile Landrover teams which brought care and treatment based on oral DDS to patients near their villages and homes. The eight Landrovers used at present over the whole country make regular stops daily at gatherings of patients, and the attendance rate at these "Landrover clinics" is higher than in static clinics. We had many opportunities of examining the patients treated by these mobile clinics, and there was no doubt that they were securing the due benefit. By the end of 1957, in the whole country some 30,000 patients were under treatment by all means and over 9,000 had already been discharged. Having seen the whole system at work, we are of the opinion that if Ghana enhances and continues its efforts *it has a good chance of being the first African country to eradicate leprosy.* We congratulate the present and previous Ghana Governments for their enlightened attitude and adequate expenditure, UNICEF for its generous participation by donating eight Landrovers and all the DDS used in therapy, all Missions for their hearty co-operation, the Ministry of Health and all members of the Ghana Leprosy Service for their faithful application to the task. It was sheer happiness to visit Ghana and see the good work done.

The establishment of the Ghana Leprosy Service is:
1 specialist leprologist in charge of the leprosy service.
1 medical officer seconded to the leprosy service.
1 senior leprosy control officer.
9 leprosy control officers (2 vacancies).
4 assistant leprosy control officers.
18 leprosy control assistants.
8 pupil leprosy control assistants (probation: 2 years).
14 drivers (9 Landrovers, 2 Volkswagen buses, 1 ambulance, 2 trucks).
1 nurse at Ankaful for the 90-bed hospital.
1 laboratory assistant.
5 office staff.

The 5 *leprosaria* are Ankaful, 500 patients, the headquarters of the service; Kokofu, for 200 patients, a new leprosarium with 60 patients so far; Ho, 100 patients, regional leprosarium for the Trans-Volta region; Yendi, 50 patients; Kpandai, 250 patients (W.E.C. Mission); Accra, 40 patients.

The regional figures for patients under treatment at December 1957 are:—

Eastern Region	2,869	(520 lepromatous)
Western Region ...	2,463	(532 ,,)
Ashanti	4,266	(420 ,,)
Trans-Volta Togoland ...	1,599	(209 ,,)
Northern Region East...	13,312	(887 ,,)
Northern Region West...	5,097	(289 ,,)
Totals ...	29,606	(2,857 lepromatous)

Leprosy Survey of Sierra Leone, 1958

Dr. C. M. Ross, O.B.E., senior leprologist in Northern Nigeria, has conducted a leprosy survey in Sierra Leone at the request of the Government, and in this was ably assisted on the field by Mrs. Ross and Mr. Alan Waudby (BELRA worker sent a short time before, who remains in Sierra Leone). This survey was carried out between 27th December, 1957, and 8th March, 1958. It is extremely valuable as it fills a gap in our modern knowledge of the leprosy endemic, and it provides a basis for an active future leprosy campaign in that country. The basic method of the survey was house-to-house or compound-to-compound visiting, and Dr. Ross examined and diagnosed all persons. In the Northern Province, 13,484 persons were examined and 763 leprosy cases found; in the South Western Province, 4,049 persons examined revealed 119 leprosy cases, and in the South Eastern Province 4,332 examined and 157 cases found. The three incidence rates are therefore 57, 29, and 36 per thousand. The estimate of the total number of existing cases is 85,000, of whom 11,000 are lepromatous. Sierra Leone has a total population of

2,038,815, an area of 27,540 square miles (about 71,000 sq. kilom.), and a density of population of 84.5 per square mile (about 33 per sq. kilom.). Missions have been the pioneers in the existing leprosy work in the country, and cover about 2,000 patients. Dr. Ross has recommended the construction of a leprosy service in Sierra Leone, including the founding of a focal base leprosarium, the training of staff, and the establishment of a clinic system, such as has been highly successful in Northern Nigeria. The hard work of Dr. Ross and his collaborators has provided Sierra Leone with the essential facts about its leprosy problem, and we look confidently to Sierra Leone for a dynamic response to the challenge of the facts, in which all interested agencies will stand ready to help.

News of Leprosy in Nepal

Dr. P. J. Chandy sends news of his experiences in Nepal. He has been there a year under the auspices of the Mission to Lepers.

Nepal is a mountainous country 50 miles long and 100 miles broad, and of high and varying altitudes above sea level. The estimated total population is 9,000,000. The capital is Kathmandu, situated in a valley at 4,500 feet (1,370 m.) and contains a population in the valley of 400,000. The inhabitants are almost entirely Mongoloid in blood. A regular leprosy survey has not been possible yet, but study has been made of patients attending a general hospital. In 1957, Dr. Chandy found 90 leprosy patients in 4,000 new cases attending for general treatment. Of these 90 cases, 40 knew that they had leprosy. He takes those who attend as an indicator of the true incidence, which therefore may be 12.5 per 1,000 of those attending hospital for various illnesses. For the whole population of the Kathmandu Valley, Dr. Chandy surmises that 10 per 1,000 might have leprosy. The neighbouring Indian provinces of Bengal, Bihar and Uttar Pradesh have much the same incidence of leprosy. Of the cases found in the Kathmandu Valley, 40 per cent were lepromatous and a fourth of the patients were females; only 2 cases were below fifteen years of age. There is considerable leprophobia and strict segregation of patents is enforced by the village headman. This is in the hilly parts; in the valley itself, the people are indifferent and make no restrictions on mixing and moving of leprosy patients. Beggars who have leprosy are required to report to the nearest Police Station and are interned at the leprosarium at Kockna, which can contain 500 patients. In Kockna, the patients are well fed and well clothed but proper medical treatment is lacking, though it certainly serves as a segregation centre for the valley. There is a leprosy officer who supervises four outpatient clinics at Pachali, Budha Nilkant, Thankot and Bhatgaon. The attendances are good at these clinics, though the sulphones have not yet been introduced. There is another segregation leprosarium at Mulungua in Western

Nepal. It is inaccessible and hard to supervise. The Mission to Lepers has been given land 11 miles south of Kathmandu to establish a modern leprosarium. His Majesty's Government, therefore, have taken a good step forward. During Dr. Chandy's experience of a year in Nepal, watching over 100 leprosy patients under sulphone treatment, he noted that lepra reactions and fevers were uncommon. There were only 2 such cases. He had not used sulphone dosage over 400 mg. per week. There had been no anaemia and no sign of toxicity. The lower dosage has been preferred because the average Nepali, though well nourished, is seldom above 100 lb. (45.3 kg.) in weight.

The Nature of the Mitsuda and the Kveim Reaction

We draw attention to the abstract in this issue (page 166) of the extremely interesting paper by KOOIJ and GERRITSEN dealing with this vital subject. From their 5 experiments, they conclude that the Kveim reaction is an expression of a sarcoid mode of reaction in certain individuals, with probably only quantitative differences in healthy perople, sarcoidosis patients, tuberculoid leprosy patients, and perhaps some other diseases; the disease sarcoidosis is a syndrome which can be evoked by many agents. Similarly the Mitsuda reaction also seems a sarcoid or tuberculoid form of foreign body reaction or an isomorphic phenomenon—a general tissue response to foreign bodies, such as leprosy bacilli and normal tissue particles. The absence of the Mitsuda reaction in the lepromatous type may be due to a fault in the reticulo-endothelial system. Certainly more study of the causes of its absence should open the way to a better understanding of leprosy.

Cancellation of the Indian Arrangements for the International Congress

The Secretary-Treasurer of the International Leprosy Association was informed on 9th June, 1958, by the Government of India that they greatly regret having to withdraw their invitation to hold the VII International Congress of Leprology in India, owing to difficulties of international political nature. The Congress therefore will not be held in India. It is too early yet to state what substitute arrangements can be made, but there is hope that it will be held somewhere this year.

LATEST NEWS 5-7-58

There is now a good chance of the Congress being held in Tokio on 12th November 1958, but final decision is awaited.

A STUDY OF THE EFFECT OF STREPTOHYDRAZID ON LEPROMATOUS LEPROSY OVER A PERIOD OF ABOUT THREE YEARS

JOHN DREISBACH, M.D.*
R. G. COCHRANE, M.D., F.R.C.P.*

In view of the fact that Isonicotinic Acid Hydrazid and Streptomycin have been shown to have an effect on the *M. leprae*, it was considered advisable to test the combination of these two drugs in leprosy. A study was started, therefore, on a group of lepromatous cases in January, 1954. In March, 1956, 4 more cases were added to this series. In all 59 cases have been studied, of which 47 will be included in this report. Those not included had insufficient treatment to be of any significance in this evaluation, but the length of treatment of the remaining 47 ranged from 10 to 40 months with an average of 32 months' treatment. During the period of experimental trial one patient died after 24 months treatment. He had shown an initial clinical improvement but after 18 months he showed a marked regression in symptoms, but in spite of all that could be done, he died some 4 months after Streptohydrazid was discontinued. Apart from this case, all the other patients continued treatment and stood the drug well.

In January, 1956, one of us (R.G.C.) returned to Kano and with the co-author made a preliminary assessment of the patients under trial with Streptohydrazid, and during this assessment it was noted that patients who had previous sulphone therapy appeared to do better than patients who had been placed on Streptohydrazid alone. Therefore, a group of cases was selected and placed on 50% Sulphetrone solution injected intramuscularly twice a week: 28 cases were placed on additional Sulphetrone by injection and 18 cases remained on Streptohydrazid alone. One case was not included in the continuation of the experiment, making a total of 46 cases. The 50% solution of Sulphetrone was chosen because in our experience heavy lepromatous cases showed less reaction and improved better under intramuscular injection of 50% Sulphetrone than with oral DDS, and it has been shown by one of us (R.G.C.), in a previous communication that parenteral Sulphetrone in the form of a 50% solution does not break down into DDS. The dose of parenteral Sulphetrone which was given was 3 ccs. of a 50% solution of Sulphetrone, intramuscularly, twice a week; that is, 3 gms. a week.

We record the following general observations. Firstly, only lepromatous cases were included in this study, and before the experiment started all cases had a complete physical examination, with a

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* The Leprosy Research Fund, 11a Weymouth St., London W.1.

biopsy, photographs, routine haematology, stool and urine examinations, and skin smears. Routine laboratory studies were repeated monthly, and the biopsies and photographs were re-taken approximately every six months. All cases which showed histologically atypical lepromatous features were excluded from this study, because it is well known that cases of the dimorphous group show a considerable tendency to spontaneous regression and, therefore, all lepromatous cases were confirmed by biopsy examination.

With the possible exception of the patient who died, there were no serious toxic manifestations. There was some evidence of erythema nodosum leprosum reactions. However, more than 50% had no such reactions during the course of the treatment. The results were as follows:—

No reactions	25
One reaction	7
Two reactions	6
Three reactions	4
Multiple reactions	5

In view of the fact that all the cases which were chosen were moderate to heavy lepromatous cases we feel that this result is significant. It is our opinion, based on many years experience with the parent sulphone, that had this been used in these cases a much higher rate of erythema nodosum reactions would have been noted. As it was, the great majority of the reactions, which were precipitated during treatment, were of such a mild nature that it was possible to continue treatment without interruption, but in a few cases of severe reaction Cortisone was administered and made possible the continuance of the treatment. In the course of the experiment the patients showed no alteration in their W.B.C. count or in the Differential count, but there was some evidence of anaemia as follows:—

No evidence of anaemia	18
Slight evidence	12
Moderate evidence	15
Marked evidence	2

All except those with marked anaemia were continued on treatment. Inorganic iron ($FeSO_4$) was added and the patients responded satisfactorily. In those with marked anaemia—that is, with less than 7.5 gms.%—the drug was stopped and more vigorous anti-anaemic measures were instituted. All were later continued in the study.

No toxic manifestations such as drug rash, hepatitis, renal impairment, dermatitis, or central nervous system complications were encountered.

General Conclusions

Most of the improvement was seen in the first 6 to 12 months. Those cases put on Sulphetrone continued to show further improve-

ment. The most noteworthy point, however, was that the mucosa of lesions healed very rapidly. Nasal septal ulcerations and nodulations, buccal, labial, lingual, and pharyngeal nodulations seemed to heal quickly—more rapidly than we would have expected with patients on sulphone therapy. In some cases healing was first noted one month after treatment began. Patients with laryngeal symptoms also improved greatly, and in two cases we saw this change on direct laryngoscopy.

In a more detailed analysis of these results it is interesting to note that there was some difference between the cases which received Streptohydrazid alone and those cases in which Streptohydrazid was combined with sulphone therapy. In the latter group of cases it did not seem to matter whether sulphone therapy in the form of a 50% solution of Sulphetrone was given continuously with the Streptohydrazid or intermittently—that is, 3 months Streptohydrazid and 3 months Sulphetrone. The following Table shows the analysis of the results in cases under Streptohydrazid alone and those given Streptohydrazid in combination with Sulphetrone:

	Improved	*Much Improved*	*Neg.*	*Period under Treatment*
Streptohydrazid alone	22%	16%	—	32
Streptohydrazid intermittent with Sulphetrone	18.5%	33.3%	—	32

SELECTION OF ILLUSTRATIVE CASES

The following four cases are selected among the 47 cases chosen for this drug trial as examples of improvement under Streptohydrazid medication. The photographs are by Dr. R. G. Cochrane and the photomicrographs by the Institute of Dermatology.

BETI MALLAMAWA, age 29 (1954), male.—Advanced lepromatous leprosy.

Case No.—Katsina 1251. See Figs. 1 and 2, 3 and 4.

Previously had Hydnocarpus treatment for five years, 1945–1950.

Commenced Streptohydrazid treatment March 1954. Placed on Intermittent Streptohydrazid treatment and continuous sulphetrone (50% parenterally) January 1956.

Patient at the time showed heavy infiltrations throughout the body and nodular lesions on the ears and face. Also marked nodulation of the tongue giving the appearance of a geographical tongue.

The patient showed marked clinical improvement between March 1954 and August 1954—and this improvement continued but at slower rate up to December 1956.

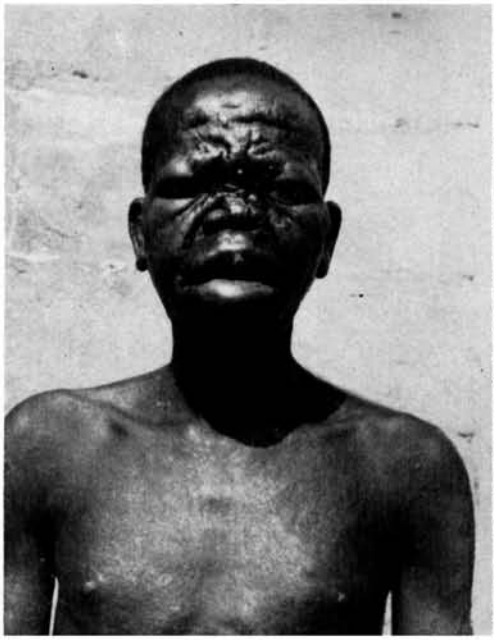

Fig. 1. Beti.

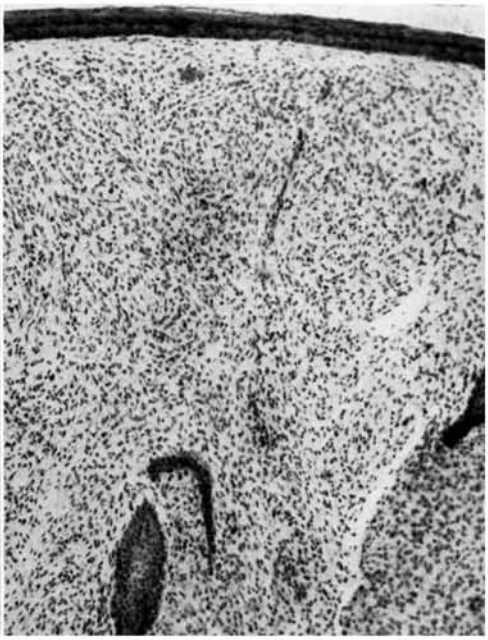

Fig. 2. Beti, before treatment.

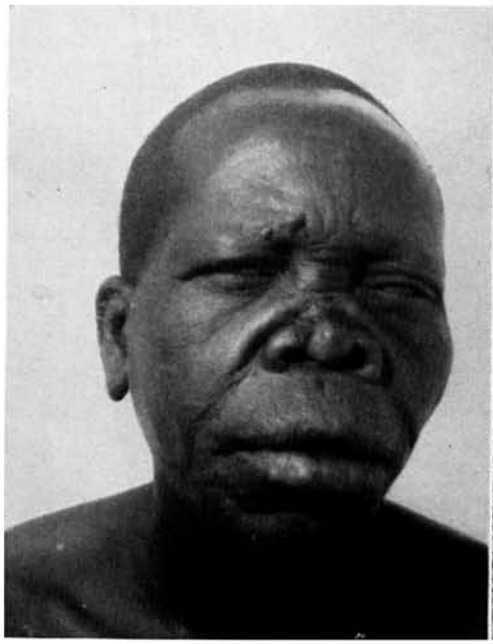

Fig. 3. Beti.

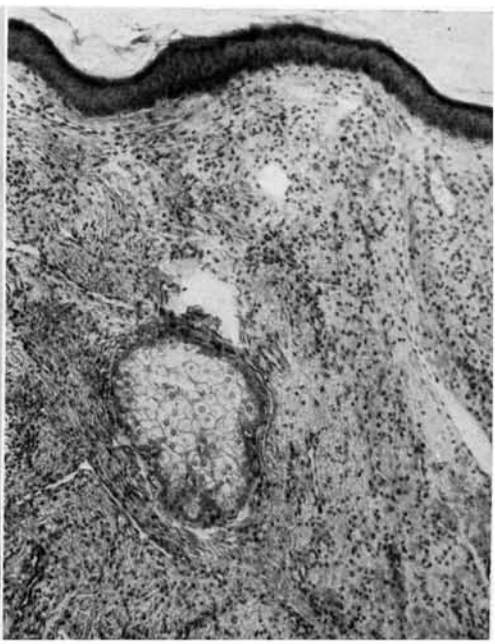

Fig. 4. Beti, after two years' treatment.

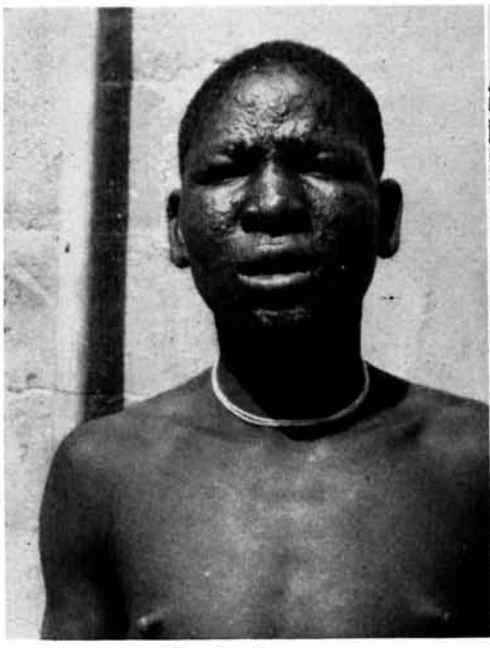

Fig. 5. Usman.

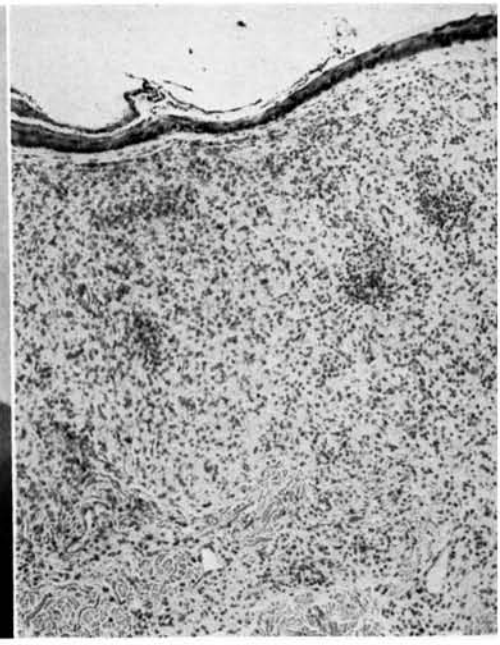

Fig. 6. Usman, before treatment.

Fig. 7. Usman.

Fig. 8. Usman, after two years' treatment.

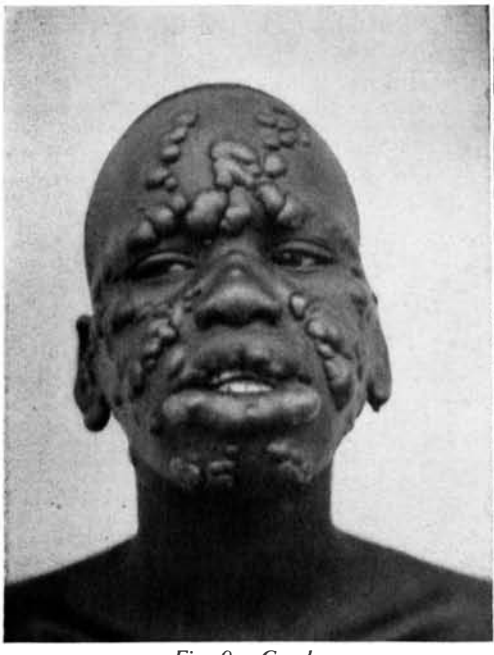

Fig. 9. Gambo.

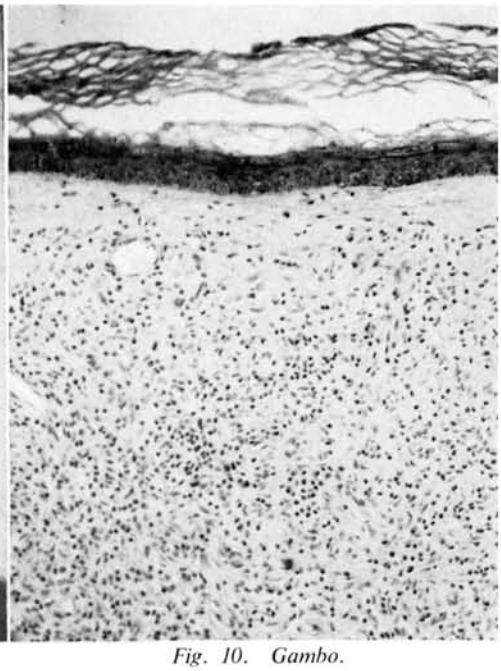

Fig. 10. Gambo.

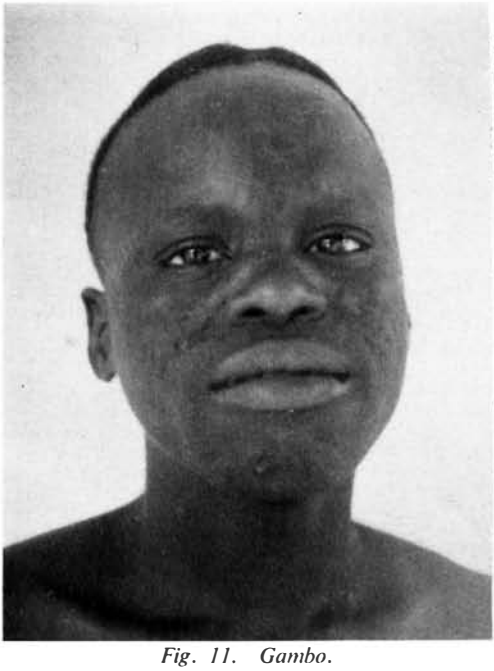

Fig. 11. Gambo.

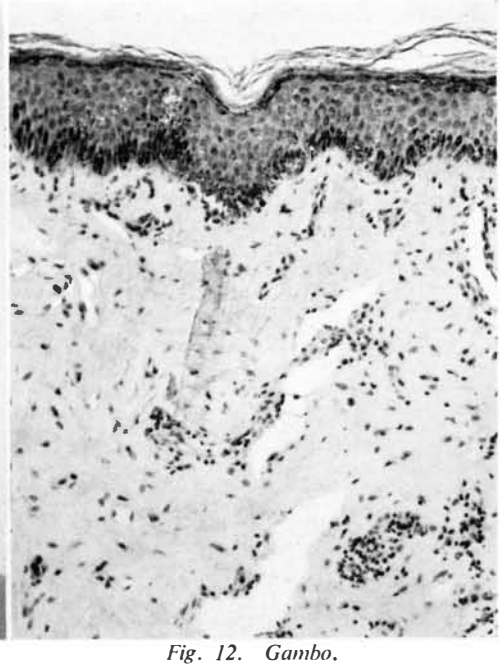

Fig. 12. Gambo.

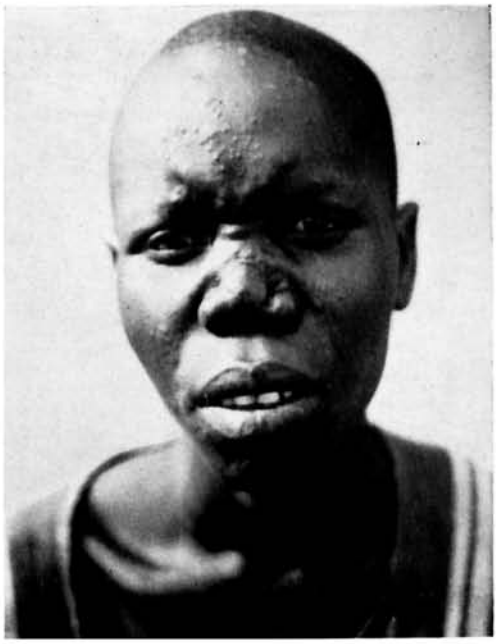

Fig. 13. Kubiya.

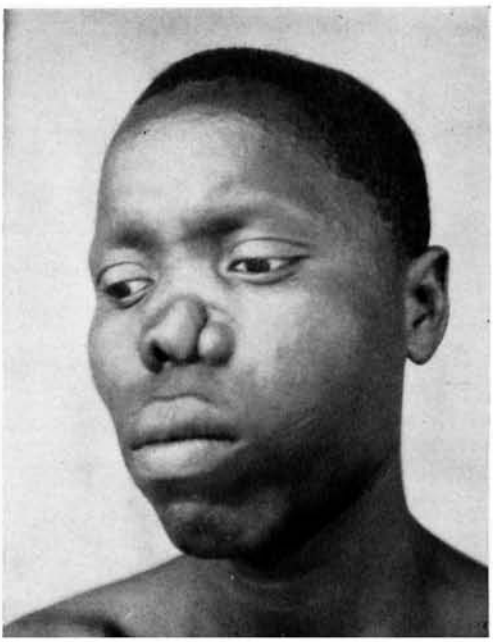

Fig. 14. Kubiya.

The following are the biopsy reports:

Biopsy of 27.3.54 (Lab. No. 1332)

The whole of the corium is filled with a massive infiltration leaving a flattened epidermis with a narrow free subepidermal zone. The infiltrate is seen to consist of macrophages which have mostly undergone foamy cell change. There are scattered giant cells but not of the Langhan's type. Many of these also show foamy cell change. Nerves are impossible to distinguish in this mass of infiltrate. Among the foamy cells is a superimposed round cell infiltration.

Section stained for acid fast bacilli (Fite Faraco technique)

Numerous acid fast bacilli showing some degree of morphological change. Bacilli are seen in all the macrophage cells including the giant cells.

Biopsy of 23.8.54 (Lab. No. 1532)

This shows a scattered round cell infiltration. The infiltrate is diffuse and in no way focalised. In addition to these round cells there are seen small areas in which there is definite foamy cell change. Nerves are clearly seen and uninvaded.

Acid fast section (Fite Faraco technique)

A few granular bacilli are scattered through the section. The bacilli are granular and stumpy looking and are also seen in the nerves.

Comment:

This is a picture of a lepromatous case resolving very satisfactorily under therapy. The residual round cell infiltration suggests some activity of the lesion.

Biopsy of 16.4.56 (Lab. No. 2148)

The superficial part of the dermis underneath the epidermis is occupied by a very narrow band of infiltrate with a clear subepidermal zone. The infiltrating cells consist of round cells and histiocytes, and there are also areas of foamy cell change. In the deeper parts of the dermis the infiltrate is very much less. There are one or two small areas of foamy cell change, otherwise there seems to be some increase of collagen but no infiltrate of any significance. Nerves when seen are uninvaded.

Acid fast section (Fite Faraco technique)

The acid fast bacilli appear to be scanty in numbers. They are scattered throughout the foamy cell areas and in the nerves.

Comment:

This is a picture of a resolving leproma which is progressing towards healing.

USMAN GARNI, age 18 (1954), male.

Katsina No. 1545. See Figs. 5, 6, 7, 8.

Previous therapy up to January 1949—Hydnocarpus oil from 1949–1954. Has been on sulphone therapy but there was no appreciable improvement.

Commenced Streptohydrazid treatment March 1954—placed on Intermittent Streptohydrazid and continuous sulphetrone January 1956.

Between March 1954 and January 1955 considerable clinical improvement.

From January 1955 to December 1956—improvement continued but bacteriological index remained moderately high and only improving from an index of 5 to an index of 4.1—but the clinical improvement was quite definite.

The following are the biopsy reports:

Biopsy of 27.3.54 (Lab. No. 1331)

The section shows all the features of a moderately advanced lepromatous case with gross foamy cell change.

Acid fast section (Fite Faraco technique)

Large numbers of acid fast bacilli throughout the section with numerous globi. The globi show a tendency to break up, and the acid fast bacilli show considerable morphological change.

Biopsy of 16.4.56 (Lab. No. 2159)

The granuloma shows considerable clearing particularly in the deeper areas of the corium. There is some infiltration underneath the epidermis leaving a clear subepidermal zone. The infiltrating cells are chiefly histiocytes and round cells and there is still some evidence of foamy cell change. The nerves are seen and are uninvaded by cellular infiltrate. There is some proliferation of the epineurium.

Acid fast section (Fite Faraco technique)

Acid fast bacilli are moderately numerous showing gross morphological change.

Comment:

This shows satisfactory commencing resolution.

GAMBO YARDAJI, age 15 (1954), male.—Advanced nodular lepromatous case. Case No. Katsina 2299. See figs. 9, 10, 11, 12.

No previous treatment.

Commenced Streptohydrazid treatment on admission in June 1954 but was placed on Intermittent Streptohydrazid and continuous sulphetrone in January 1956.

At the time of admission the patient showed multiple confluent, large firm nodules—particularly on the face and ear lobes, although the whole of the trunk was affected.

Between June 1954 and December 1956—very marked clinical improvement with an almost 30% improvement in the bacteriological index.

During the course of treatment patient showed no reactions and the progress was maintained.

The following are the biopsy reports:

Biopsy of July 1954 (Lab. No. 1450)

The whole of the corium is occupied by a closely packed mass of granulomatous tissue. The infiltrate consists chiefly of histiocytes and near the epidermis there are several multinucleated cells, there is some evidence of foamy cell change, but this is not conspicuous. Nerves when seen are not invaded, and there is a well-marked vascular free subepidermal zone.

Acid fast section (Fite Faraco technique)

Very large numbers of acid fast bacilli throughout the section, many of which are beaded and darkly stained, but morphological change is no more than to be expected with such a large number of bacilli.

Biopsy of 17.12.56 (Lab. No. 2426)

There is scattered round cell and histiocytic infiltration of slight intensity diffusely distributed throughout the upper parts of the corium and extending up towards the epidermis, but there is evidence of a clear sub-epidermal zone. Cellular infiltrate consists chiefly of histiocytes and round cells. There is no significant evidence of foamy cell change. Again, the section is a poor one for nerves, but one nerve is completely uninvolved by infiltrate.

Acid fast section (Fite Faraco technique)

Very few acid-fast bacilli seen on careful search. An occasional granular bacillus is recognisable.

Comment:

This is a lepromatous case which has responded extremely well under therapy.

Biopsy of 3.6.57 (Lab. No. 2761)

The granulomatous infiltration has very appreciably decreased. There is only slight to moderate infiltration underneath the epidermis leaving a clear subepidermal zone. In the deeper parts of the dermis the granuloma has almost completely cleared. The infiltrating cells are chiefly histiocytes, some round cells and an occasional plasma cell. Nerves in the dermis are well seen and are uninvaded and many show marked proliferation of the epineurium. There is some evidence of foamy cell change although this is not marked.

Acid fast section (Fite Faraco technique)

There are acid fast bacilli throughout the section but these are very scanty in numbers. They are seen in the histiocytes and in the nerves. Acid fast bacilli in the nerves show no morphological change.

Comment:

This shows marked resolution of the lepromatous infiltration.

KUBIYA GAYA, age 20 (1954), male. Kano—4186. See Figs. 13 and 14.

No previous treatment recorded.

Commenced Streptohydrazid on May 10, 1954, and placed on Intermittent Streptohydrazid and parenteral Sulphetrone January 1956.

The patient is a well-developed, well-nourished male with definite nodular lesions on the ear lobes and face. Nasal septum ulceration and partial collapse, with partial blocking of the airway. Moderate buccal labial and mild laryngeal involvement. The lesions on the trunk are elevated erythematous plaques with discrete sloping margins and show considerable wrinkling. Lesions on the face are definitely lepromatous and those on the trunk are suggestive of dimorphous leprosy.

From May 1954 to January 1955 the clinical improvement was slight—but from January 1955 to December 1956 the improvement was more marked.

In November 1955 there was histological evidence of a reaction and in January 1956 there was a mild lepra reaction following a tuberculin test.

Biopsy of 8.7.54 (Lab. No. 1417)

The whole of the corium is occupied by massive granulomatous infiltration which extends deeply into the dermis. There is very clear free subepidermal zone. The granuloma consists almost entirely of large macrophages many of which show foamy cell change. Here and there are some plasma cells but these do not show significant increase. Nerves when seen are uninvaded with some proliferation of the epineurium.

Acid fast section (Fite Faraco technique)

Large numbers of acid fast bacilli throughout the section with some globus formation. The bacilli show no morphological change.

Biopsy of 14.11.55 (Lab. No. 1955)

The general overall picture is that of a moderate leproma. There is scattered infiltration throughout the corium although this is not seen in a continuous band as is often the case in advanced lepromatous leprosy. The subepidermal zone is clear and vascular but amidst this general lepromatous infiltrate which is only moderate in intensity, there is a superimposed more acute inflammatory process, and in some areas this is intense for there are very numerous round cells, the majority of which are polymorpho-nuclear leukocytes. There is also an increase in plasma cells. There is considerable vascularity throughout the section but there are no marked pathological changes in the vessels. Nerves when seen are uninvaded and have the appearance of lepromatous leprosy.

Acid fast section (Fite Faraco technique)

Numerous acid fast bacilli showing morphological change in the areas which are not affected by the acute inflammatory response. In these latter areas the bacilli are very scanty and are almost absent.

Comment:

This appears to be an acute process of the nature of erythema nodosum superimposed upon moderately advanced lepromatous leprosy.

Biopsy of 17.12.56 (Lab. No. 2395)

This shows a very considerable decrease of the granulomatous infiltration which is only slight to moderate in intensity and chiefly in the upper parts of the dermis near to the epidermis there is a relatively clear subepidermal zone. The granulomatous infiltration consists almost entirely of foamy cells. There is some round cell infiltration and some increase of plasma cells. Nerves when seen are relatively uninvaded and show some increase in the cells of Schwann.

Acid fast section (Fite Faraco technique)

The number of acid fast bacilli appear to be considerably reduced but they are still seen in significant numbers and the interesting feature is that in the epidermis lining the hair follicles there are masses of acid fast bacilli in among the epidermal cells. Nerves also show numerous acid fast bacilli.

Comment:

This is a lepromatous case which is responding satisfactorily to therapy. The granuloma is beginning to clear but the numbers of acid fast bacilli although reduced, still seen in appreciable quantities.

In view of this result it would indicate that there is a more rapid improvement on a combination of sulphone therapy and Streptohydrazid than with either alone.

One of the interesting points to which we would like to draw attention is the very marked improvement in nasal and buccal lesions. It is further interesting to note that 3 cases of clinically diagnosed pulmonary tuberculosis were also included in this study. These all had advanced lepromatous leprosy as well. No X-ray examination or culture of the bacilli was possible, but the diagnosis was made on clinical findings and on positive sputum. The acid-fast bacilli could possibly have been *M. leprae* coughed up from the larynx, but the pulmonary condition cleared with the first year of treatment and the sputum became negative, whereas the skin continued to be positive to *M. leprae*. None now show clinical evidence of tuberculosis.

Conclusions

We conclude by this experiment that Streptohydrazid in a dosage of 5.6 gms. per week, given preferably in combination with sulphone therapy, is a method of treatment which we can advocate for the rapid clearing of nasal and buccal lesions, and for those cases which show intolerance to sulphone therapy. When this intolerance is very great we would recommend that Streptohydrazid be given alone for the first year, and then Streptohydrazid and parenteral Sulphetrone be given for the second year. As a result of the above conclusions we have chosen cases for further clinical trial to see whether finally they will become negative to all routine tests more rapidly than similar cases on the parent sulphone or on Sulphetrone when given alone.

Acknowledgments

We would thank most sincerely Messrs. Chas. Pfizer & Co., for their generosity not only in supplying the Streptohydrazid for this clinical evaluation but also Cortisone, and our thanks are especially due to Dr. Gladys Hobby for advice and assistance throughout the experiment.

'VADRINE' (S.131) IN THE TREATMENT OF LEPROMATOUS LEPROSY: A PRELIMINARY REPORT

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In 1956 Dr. H. Brodhage drew our attention to the possible anti-leprosy action of two new oxdiazolones which had been shown to have tuberculostatic activity in guinea pigs equal to that of isoniazid and to be less toxic (Brodhage and Wilder Smith, 1955). One of these compounds, the p-aminosalicylate of 2-pyridyl-(4)-1,3,4, -oxdiazolone-(5), had been shown to be active *in vitro* against isoniazid-resistant strains of *M. tuberculosis* and according to Dr. P. Geistlich (personal communcation) had proved to be non-toxic to humans in tuberculosis trials and had shown activity against leprosy in a preliminary trial in Angola.

It was decided to carry out a trial of this compound in a small number of leprosy patients at the Jordan Hospital, and a supply was sent to us by Edward Geistlich & Sons, Wolhusen, Switzerland, who had manufactured it in their Research Laboratories under the name S.131 later to be changed to Vadrine.

Method

Seven consecutive patients admitted during a period of nine months were treated with Vadrine and have now been observed for periods of 9-18 months. Five had had no previous treatment, one had been treated with dapsone (DDS) from 1947 to 1954, and one had been taking dapsone for 9 months immediately prior to admission to the Jordan Hospital. All seven patients were proved to be suffering from the lepromatous type of leprosy and had no atypical features clinically or histologically. Bacilli were very numerous in all.

Vadrine was supplied in the form of tasteless yellow tablets of 200 mg., and we decided to commence with one tablet daily, to increase by one tablet every 6 days up to a maximum dosage of 40 mg./kg. of body weight, and to continue at this level. Five patients have completed one year's treatment or more, the remaining two having had treatment for only 9 months.

Results

This paper is mainly concerned with the results of treatment during the first year, since only 3 patients have exceeded one year's treatment and one of these has had a restricted dosage owing to *erythema nodosum leprosum.*

Clinical Observations. Patient No. 1 is a Eurasian (Anglo-Indian) female, aged 46, who gave an 18 months' history of skin lesions. At the time of admission she was found to have large

numbers of erythematous macules and infiltrated lesions on face, buttocks and limbs, the face appeared puffy, the nose was broadened and the nasal septum was ulcerated. Improvement has taken place steadily with disappearance of all lesions by the end of one year leaving light brown marks on the skin, and there has been no clinical deterioration during the ensuing 6 months. Nasal ulceration healed after 2 months' treatment. Early changes of keratitis developed in the eyes during the first 6 months and have remained unchanged. Mild, non-febrile *erythema nodosum leprosum* commenced 7 months after commencement of the trial and has recurred ever since. This has not called for any special treatment, nor has it necessitated any reduction in dosage of Vadrine.

Patient No. 2 is an Italian female, aged 24, and is the only one in the series who has had known contact with leprosy; her father was treated for lepromatous leprosy when she was a child. She says that she noticed her first skin lesions at the time of the birth of her baby one year prior to admission here. On admission there were many erythematous macules, infiltrated lesions, papules and nodules on face, arms, buttocks and thighs, she had early keratitis in both eyes, and the nasal septum was ulcerated. A number of new lesions appeared on both legs about 3 months after commencing treatment, and during the following 9 months there was slight but definite clinical improvement. The appearance of eyes and nose remained unchanged. Between 12 and 15 months her lesions began to look active again, the nasal mucosa looked worse and the eyes developed more obvious corneal changes.

Patient No. 3 is a Eurasian (Anglo-Burmese) male, aged 32, who noticed his first leprosy lesions one year prior to admission here and commenced sulphone therapy in Burma 3 months later. Dapsone was stopped prior to commencing treatment with Vadrine, and examination revealed many macules, papules, nodules and infiltrated lesions. Slight but definite clinical improvement has occurred but has been somewhat masked by severe *erythema nodosum leprosum* which commenced 3 months after commencing Vadrine. It recurred in bouts for the next 6 months and has been continuous after that. Large doses of prednisone have been required to keep the reaction under control, and the dosage of Vadrine has been reduced.

Patient No. 4 is a German lady, aged 49, whose first lesions appeared 6 months previously. On admission here she had very large numbers of erythematous macules and infiltrated lesions over face, trunk, buttocks and limbs, the face was puffy and the eyes showed early changes of keratitis. After 6 months' treatment all the macules disappeared, the infiltrated lesions had flattened, and there was no longer any oedema of face. By the end of one year the skin had become completely normal in appearance and the keratitis had much improved. There has been no clinical deterioration during the

ensuing 3 months. Her gall-bladder was removed for calculi 9 months after commencing the trial, and Vadrine was continued without interruption.

Patient No. 5 is a Euro-African male from British Guiana, aged 24, who gave a two years' history of skin lesions and increasing numbness of hands and feet. On admission he had leonine facies, infiltrated lesions on limbs and buttocks, nasal ulceration, early keratitis, and anaesthesia of all four limbs. By the end of one year the thickening of the face has improved and the lesions on the rest of the body have flattened, but nasal ulceration is still present. Keratitis has remained unaltered.

Patient No. 6 is a Eurasian (Anglo-Indian) male, aged 27, who noticed skin lesions 6 months prior to admission here. He was found to have multiple small erythematous macules and infiltrated lesions on buttocks and limbs, and the eyes showed early changes of keratitis. He has completed 9 months' treatment and all the skin skin lesions have flattened and become purple-brown in colour. The eye changes have not altered. Treatment for intestinal amoebiasis was successfully carried out concurrently with the trial, and no ill-effects were encountered.

Patient No. 7 is a Eurasian (Anglo-Indian) female, aged 57, who was treated for leprosy in India with sulphones from 1947 to 1954. Treatment then ceased, and 3 years later fresh lesions appeared. When she was examined here she had enormous numbers of erythematous nodules and infiltrated lesions over back, abdomen, buttocks and limbs, the skin of the face and nose was diffusely thickened, the ear lobes were pendulous, the eyes showed changes of keratitis and there was anaesthesia over all four limbs. Between the 1st and 24th week of treatment with Vadrine many of the more prominent nodules became necrotic and ulcerated, followed by healing. After 9 months' treatment the skin of the face has become markedly less thickened and many of the skin lesions have become flatter. The keratitis has not changed.

If clinical observations during the first year of treatment with Vadrine are compared with the results we would have expected from sulphones, it can be said that results with patient No. 4 have been considerably better, with No. 1 slightly better, with Nos. 3, 6 and 7 on a par, and with Nos. 2 and 5 slightly worse. The failure of nasal ulceration to heal in patients 2 and 5 is significant.

The development of early keratitis in patient No. 1 and the persistence of keratitis during the first year of treatment in Nos. 2, 5, 6 and 7, are in keeping with what we would expect from sulphone therapy at this hospital. Similarly, the ulcerating nodules in patient No. 7 during the early stages of treatment and the onset of *erythema nodosum leprosum* in No. 3 are developments which might have occurred with sulphone therapy.

Apart from slight anaemia occurring in patient No. 1 six weeks after commencing treatment, which responded to iron, the absence of side-effects has been striking.

Bacteriological Progress. Bacteriological progress was assessed at 3-monthly intervals from the bacterial index of skin smears and also from skin biopsies (Ridley, 1958). No significant alteration was to be expected in the bacterial index of smears, and none was seen; this index seldom alters in lepromatous patients of European or Eurasian origin during the first year of treatment with sulphones. The biopsy index did not alter significantly during the first 3 months, but at the end of 6 months the mean value for the 7 patients had fallen by 23%, and by the end of 12 months (4 cases only) it had fallen by a further 31%. The mean fall throughout the year was 26% per period of 6 months, compared with 25% which was the figure obtained from a larger series of similar cases on sulphones. The method of calculating these results was given in the earlier paper (Ridley).

The period of treatment under review, one year, is too short to obtain an accurate assessment of the progress of each individual patient since there is considerable random variation between biopsies, but in general the results agree with clinical impressions. In patient No. 4 who responded very well clinically, the index fell at twice the average rate; in patients 2 and 5 who showed a rather poor clinical response, the index in No. 2 fell at the usual rate up to the end of the year, only to rise again at the end of 15 months' treatment when solid-staining forms of bacilli reappeared in the skin lesions, and in No. 5 the index did not alter significantly during the year and the bacilli never became properly granular. These two patients therefore must be considered to have responded poorly. In all the other patients the bacilli became granular after 3 months' treatment.

Of other laboratory tests, the serum globulin level was raised (over 3.0 g./100 ml.) in five of the seven patients on admission, and in three of them it had returned to normal (2.5 g./100 ml. or lower) at the end of one year's treatment. In the other two patients (Nos. 1 and 5) both total globulin and gamma globulin levels remained high. The erythrocyte sedimentation rate appeared to be of no value. Other tests failed to detect any leucopenia or any diminution of hepatic or renal function which could be ascribed to the drug. In one patient the haemoglobin percentage dropped slowly from 86% to 72% during the early stages of treatment, but gradually returned to the pre-treatment level, without interrupting treatment, with the addition of oral iron.

Conclusions

As far as can be judged from a small series of cases, Vadrine appears to be a non-toxic drug, which during the first year of treatment, has a potency equal to that of sulphones. Not all patients

responded equally, however, and whereas one responded exceptionally well, in two it was thought advisable to discontinue the drug at the end of one year or 15 months. It is not yet possible to say whether these failures indicate an individual variation in the response to Vadrine or whether they are part of a general pattern of drug resistance developing towards the end of a year. A further analysis of the results will be made on completion of the trial.

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'VADRINE' (S.131) ASSESSED BACTERIOLOGICALLY IN THE TREATMENT OF EXPERIMENTAL MURINE LEPROSY

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The tuberculostatic action of the p-amino-salicylate of 2-pyridyl-(4)-1,3,4-oxdiazolone-(5) ('Vadrine'—Research Number of Edward Geistlich Sons Ltd., Wolhusen 'S. 131') has been described by Wilder Smith, (1954) and by Brodhage and Wilder Smith, (1955). The *in vitro* efficiency of 'Vadrine' against the Tb. strain H 37 Rv is within 1:2,560,000. In attempts to produce *in vitro* resistant variants it was observed after 18 sub-cultures that resistance of the tested strain H 37 Rv to 'Vadrine' had in no way increased (Brodhage and Wilder Smith, 1955; Brodhage, 1955). This fact, coupled with the slight toxicity, seemed sufficient justification to test the effect of 'Vadrine' on leprosy. To this end, using 4:4′diaminodiphenyl-sulphone (DDS) as a control, we examined the effect of 'Vadrine' in the treatment of experimental leprosy in the rat.

In view of the impossibility of transferring human leprosy to suitable test animals, murine leprosy is the best experimental infection on which new substances intended for the treatment of human leprosy can be tested (Carpenter, 1951). A final assessment on the antileprous effect of a substance can of course only be made on the results obtained in treating leprosy patients. Bearing in mind these limitations we give the following account of the bacteriological results of the animal tests we carried out.

Material and Method

Forty-five white rats (weight about 100 g.) were infected intra-testicularly with a suspension of *Myc. leprae murium*, strain 'Wells'. (This strain was kindly put at our disposal by Dr. G. R. F. Hilson, St. George's Hospital, London).

The infection dose was about 0.02 ml. (about 250,000,000 bacilli) in physiological saline solution + 5% bovine albumin fraction V (pH = 7.0). The animals were divided into three groups (each containing 15 rats) receiving either no treatment or treatment with DDS or 'Vadrine'. A further 15 animals were intratesticularly infected with the same dose of heat treated (5 mins. at 100° C.) murine leprosy bacilli.

The substances to be tested were mixed in their pure state with the rat food, in the amount of 0.2% DDS and 1% 'Vadrine' that is based on the relative dosage of DDS in leprosy and of 'Vadrine' in tuberculosis. Treatment commenced 21 days after infection. At the end of one year the test animals were killed.

The efficiency of the tested substances was judged on the basis of the following criteria:

1. Size of the testis (length, breadth and depth) and the spleen (length and breadth).
2. Bacterial index of tissue suspension of lung, liver and spleen according to the following schedule:

Bacterial Index	*Number of Bacteria*	*Number of Fields**
5	more than 100	1
4	10 —100	1
3	1 — 10	1
2	1 — 10	10
1	1 — 10	100
0	none	100

* Oil immersion and x 10 binocular.

3. Number of bacteria per ml. testis homogenate. The method chosen was the Hilson (1956) modification (Hilson and Elek) of the technique devised by Hobby et al (1954).

1. Preparation of stained slides.

(*a*) A suitable dilution of homogenate is required to provide, when the technique has been completed, an average of between 5 and 15 bacilli per counting area under the microscope. The diluting fluid must be proteinous in nature, and formalin-milk is used. A 25-ml. screw-cap universal container is filled with milk and spun in an ordinary laboratory centrifuge at 2,500–3,000 r.p.m. for 15 mins. to bring the cream to the top. A Pasteur pipette is introduced into the subnatant milk and the latter drawn off leaving the cream behind. 10 ml. of this defatted milk and 1.5 ml. formalin (40% HCHO in water) are brought to 100 ml. with distilled water and thoroughly mixed. This constitutes the diluting fluid: if one has no preliminary idea of the likely bacillary concentration, it may be convenient to make up 1:10, 1:100 and 1:1,000 dilutions of the homogenate. The dilutions are well shaken to produce even mixing.

(*b*) An 'Agla' micrometer syringe (Burroughs Wellcome) is fitted with a needle (Record fitting) slightly larger than that usually supplied with the syringe with the pointed end ground square. The larger bore avoids blocking with minute tissue fragments and the square end allows better control of the small drops which are formed at the tip.

(*c*) The syringe, detached from the micrometer holder, is filled and emptied twice with the dilution and finally filled with about 1cm. length of fluid. It is then fitted into the micrometer holder and the handle turned to expel a few drops and to set it to the zero mark, and the end of the needle is touched inside the fluid container to

detach the last drop. The black screw on the holder is tightened a little to provide a moderate braking action on the handle.

(*d*) Slides are cleaned and flamed in the usual way to render them grease-free. One slide is used for each dilution. The micrometer handle is turned so as to extrude 1 microlitre of fluid (one complete turn of the handle extrudes 0.01 ml.; turning it through only 5 of the smallest divisions on the handle delivers 1 microlitre); this is touched on to the corner of the slide to set up standard conditions at the needle tip and this drop is not considered further. Five more drops are then placed at the centre of the slide, in a row of 3 and a row of 2, being set just far enough apart to avoid their running into each other. Without delay the slide is placed on a piece of white paper carrying an ink outline of a square of side 0.5 cm. Each drop in turn is brought over the square and spread to the same area with the end of a straight platinum wire (the operations of placing the drops on the slide and spreading them must be done quickly to prevent irregular distribution of bacilli due to drying). The slide is then placed on the levelled lid of a boiling waterbath for about 1–2 mins. to dry and fix the films. The slide is taken off, allowed to cool and flooded with phenol-gelatin solution which consists of 0.5% gelatin and 0.5% phenol in distilled water. The solution is then poured off the slide which is allowed to drain for 2 or 3 seconds and then placed on the water-bath lid again for 2 minutes. The slide is then held in formalin vapour for 3–5 mins, placed on the lid again to drive off formaldehyde vapour and stained by Ziehl-Neelsen method. Naked-eye examination should confirm that the centre of each square film is thicker and more deeply counter-stained (counter-staining with Loeffler 1:5 for 30 seconds should be very light) than the periphery; if the thickest part is deviated away from the centre, there may be an incompletely homogenized particle causing distortion or the water-bath lid may not be level. Inaccuracy will follow. A deeply-stained ring within a square indicates that too much drying occurred before the drop was spread to its square form; a lightly-stained ring is often found on warm dry days and is not a serious cause of error.

(*e*) Ten fields are counted across the equator of each drop in the following way. The lower, or nearer, edge of the drop is found under the microscope (oil-immersion 2 mm. objective) and then, using the stage micrometer, the stage is moved down, or nearer by 2½ mm. which brings the field on to the equator of the drop. The slide is then moved right or left until the edge of the drop is again found and the moving stage adjusted if necessary so that the stage micrometer registering lateral movement is set at a division of exactly midway between two divisions and the microscope field is just inside the spot edge. The bacilli in this field are counted and then those in 9 other fields, found by traversing the stage by ½ mm. intervals and the average count per field calculated. The last field should be just

within the opposite edge of the drop; if the latter has been spread rather small, it may lie outside and the average of the 9 fields counted should be taken. The counts increase, of course, as the thicker centre is approached and diminish again towards the opposite edge. The "grand average" count per field for all 5 drops is determined and the numbers of bacilli per ml. of dilution are found by the calibration factors set out below.

2. Calibration of microscopes and calculations

Bacilli may be counted in the whole circular field (Hilson, 1956; Hilson and Elek) within the area of an eyepiece graticule or using a square eyepiece mask as in reticulocyte estimations. Whichever is chosen, it must be calibrated, most conveniently by examining the smallest square of a Neubauer (or other) haemacytometer chamber with the same oil-immersion lens as is to be used for the counting. To visualise the lines, the haemacytometer ruled area is not covered with a cover-slip, the lens is used dry and the microscope condenser is racked well down. Hilson found with his objective and × 5 binocular eyepieces that the field corresponded to 4 smallest squares (1/100 sq. mm.).

Calculation: 1/1000 ml. of material is spread over an area of 25 sq. mm. giving an average volume of 1/25,000 ml. per sq. mm. Each field has an area of 1/100 sq. mm. giving the volume per field as 1/2,500,000 ml. Therefore the numbers of bacilli per ml. of dilution examined (N) = average count per field (n) × 2.5 × 10^6. Obviously this must be multiplied by the dilution factor to arrive at the numbers of bacilli in the original homogenate.

(Note again, that for maximum accuracy n should be between 5 and 15).

Specimen: Counts: Drop 1: 4, 2, 4, 12, 13, 10, 15, 10, 8, 4; mean 8.2
Drop 2: 0, 3, 9, 17, 15, 13, 11, 12, 3, 1; mean 8.4
Drop 3: 1, 6, 2, 15, 14, 14, 14, 8, 2, 1; mean 7.7
Drop 4: 2, 3, 5, 14, 12, 12, 10, 3, 0, 1; mean 6.2
Drop 5: 5, 8, 7, 11, 5, 12, 12, 9, 5, 2; mean 7.6

mean 7.6

Dilution of homogenate: 1:30;

Bacilli/ml. of homogenate = 7.6 × 2.5 × 30 × 10^6
= 570 million.

It should be mentioned here that with the technique applied, no distinction is made between living and non-living bacilli. The number of bacteria found and calculated are derived from those micro-organisms that were stainable (Hanks, 1951; Hobby et al, 1954).

Test Group	No. of animals	Testis (cm.)			Spleen (cm.)		Bacterial Index				Bacteria per ml. testis homogenate	*Ratio
		Length	Breadth	Depth	Length	Breadth	Lung	Liver	Spleen	Mean		
(1) Controls untreated ...	15	2.2	1.2	0.8	4.6	1.1	1.3	1.3	1.4	1.33	1,304,885,000,000	0
(2) DDS 0.2 % in the food ...	13	2.0	1.1	0.8	5.5	1.3	0.6	0.1	0.4	0.37	19,939,980,800	65
(3) 'Vadrine' 1.0% in the food ...	10	1.6	0.8	0.5	3.9	0.8	0.2	0.2	0.3	0.23	1,631,000,000	800
(4) Controls infected with heat-treated bacilli (5 mins. at 100° C.) ...	7	1.7	0.9	0.6	4.1	0.7	0.4	0.8	0.4	0.53	2,257,643,000	578

$$* = \frac{\text{No. of Bacteria per ml. Testis Homogenate Control Group (1)}}{\text{No. of Bacteria per ml. Testis Homogenate Test Group 2, 3 or 4}}$$

Results

The results obtained in the animal tests are summarized in the table. These are expressed in simple average figures which were calculated for the individual test groups.

Fifteen rats died from non-specific infections during the course of the experiment.

It is shown in the summarized average figures that DDS and 'Vadrine', which were both mixed as pure substances with the food, exert a marked therapeutic effect on experimental leprosy in the rat. This is revealed in the average size of the testis and the spleen with the exception that the spleen in the animals under DDS is larger than that of the untreated controls. The bacterial index, calculated from the number of bacteria present in tissue suspensions of lung, liver and spleen, shows an average total degree of infection in the untreated controls of 1.33 as compared to 0.37 in the DDS, 0.23 in the 'Vadrine' and 0.53 in the group infected with heat treated bacilli.

A comparison of the average number of bacteria per ml. testis homogenate clearly reveals the effect of DDS and 'Vadrine'. With an infection dose of about 250,000,000 bacilli, the calculated number of bacteria per ml. testis homogenate indicates that neither DDS nor 'Vadrine' are able to destroy the murine leprosy bacilli. Both substances, however, inhibit the increase of the micro-organism to a marked degree as is demonstrated by a comparison with the untreated control group. With the test series as arranged by us, and the dosage chosen, 'Vadrine' has proved to be more efficient than DDS.

Hobby et al, (1954) also observed that in the tissue suspensions of animals (lung, liver and spleen), bacteria could be demonstrated in the animals which had been infected with heat treated suspensions *Myc. leprae murium*. The question of whether this is due to the transport of non-living micro-organisms of these organs or to the fact that heating for 5 mins. at 100° C. is inadequate to destroy all the bacteria is left open by the authors. According to the findings reported by Naguib et al, (1956), the latter possibility is the more probable. In tests carried out by these authors (intracorneal injection in the mouse) even suspensions of *Myc. leprae murium* heated to 60° C. for 120 mins. caused typical lesions although only after a prolonged latent period of up to eight months.

Elek and Hilson (1956) assume that non-living lepra bacilli are taken up by tissue phagocytes and remain demonstrable by staining for long periods. Four months after intraperitoneal infection of white rats these authors were unable to distinguish any difference (number of bacteria, histological changes) between the animals which had been infected with living murine leprosy bacilli and those infected with heat treated bacilli. Our own results, i.e., the number of bacilli per ml. testis homogenate in the group infected with heat treated organisms is significantly lower than that of the control group,

although it is larger than should be assumed on the basis of the amount injected. Provided the technique of our heat treatment is correct, it must be assumed that this treatment did not destroy all the bacilli. This may have permitted a certain proliferation of bacilli. It is expressed by a larger number of bacteria per ml. testis homogenate compared to the injection amount. It would appear therefore that our observations support the opinion of Naguib and his associates.

Summary

The treatment of experimental murine leprosy in the rat with 4:4 'diaminodiphenyl-sulphone (DDS) and p-amino-salicylate of 2-pyridyl (4)-1,3,4-oxdiazolone-(5) ('Vadrine') under our test conditions and with the chosen dosage reveals a marked therapeutic effect of both substances. 'Vadrine' would appear to be more efficient than DDS. The test results obtained in animals infected with heat-treated suspensions (5 mins. at 100° C.) of murine leprosy bacilli give rise to the suspicion that either our technique for the heat-treatment was incorrect or that this treatment is insufficient to destroy all the bacilli.

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HISTAMINE IN THE BLOOD IN LEPROSY

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At various national and international conferences there has been meticulous and prolonged discussion of the classification of leprosy, but none has been evolved to suit all opinions. There has been wide agreement about the existence and polar position of the lepromatous and tuberculoid forms, because each has a distinct clinical, pathological, and immunological picture. The immunology is not well understood. In the classical cases of tuberculoid leprosy the lepromin test is strongly positive, while in the lepromatous it is negative, and a theory was propounded that the positivity of the test indicates "allergy" and the negativity "anergy" (Rotberg, 1939; Davey, 1946). Still it is not quite clear whether positivity indicates allergy or potential allergy. Lepra reaction, which is an important and interesting phase which can supervene in the clinical course of leprosy is also thought by some to be of allergic nature. Various arguments for and against theories of allergy are put forward from time to time but remain speculative because of the failure to cultivate *M. leprae* in artificial media and to inoculate it successfully in experimental animals.

It has long been recognised that histamine plays a very important role in anaphylactic shock and in such human allergic reactions as urticaria and hay fever. Åke-Nitzen (1947) observed derangements of the histamine content of the blood in cases of arsphenamine dermatitis and of chronic recurrent urticaria. Hence it was thought worth while in leprosy to study the subject biochemically, and to estimate the histamine content of the blood.

Material and Methods

Most of the blood samples were collected by venipuncture from leprosy patients at the Sassoon Hospitals, Poona, and from blood donors to the blood bank at the same hospitals. All subjects came from a particular type of socio-economic group, so there was stratified sampling, and samples from the leprosy and non-leprosy group could reasonably be compared. The sampling was done at random, and the samples were taken after a vegetarian breakfast at about 10 a.m. and sent within the hour in an ice chest to the laboratories. Most of the samples were taken from males aet. 19 to 34 years and a few from non-pregnant adult females. Clinical records have been maintained of all subjects of the study, with haemograms and the results of serological tests for syphilis. There were 75 non-leprosy and 68 leprosy subjects.

The method used for the estimation of the histamine of the blood was a combination of those of McIntire et al. (1947) and Lubschez (1950), and the steps were as follows:—

1. Extraction of histamine from the sample in n-butanol;

2. Adsorption of histamine from n-butanol on cotton-acid-succinate;
3. Elution and colorimetric estimation of histamine in its purified form.

This microchemical method is suitable for the estimation of histamine base in amounts of the order of 0.01 to 0.1 microgram or more per cc. of sample. The substance extracted from the blood by this method was identified chemically as histamine. It was then tested for its pharmacological action in the experimental animal (the dog), where it behaved like histamine in producing a fall in blood pressure. Its effects were counteracted by the antihistaminic drug anthisan (Messrs. May & Baker, India, Ltd.). Quantitative pharmacological and chemical estimations agreed well. The results of the study are presented in the Table.

Results and Discussion

In the non-leprosy cases the mean histamine level in the blood has been 4.84 microgram of histamine base per 100 cc. (all the values are expressed in terms of histamine base): in the leprosy subjects it was 7.01 microgram per 100 cc. (see Table). In order to assess the difference between the two groups, Student's t-test was applied to the values obtained and the value of "t" was found to be highly significant (3.045). The histamine levels are significantly higher in leprosy subjects.

TABLE OF FINDINGS

No. of Subjects and Type	Means (in micrograms per 100 cc. blood)	Standard Deviation	Range	Coefficient of Dispersion	Results of t-test for significance of difference of means
78 non-leprosy	4.84	3.3	0.4 to 13.6	0.68	
68 leprosy	7.01	5.2	0.6 to 24.4	0.74	Highly significant
21 lepromatous	6.94	4.3	1.3 to 17.8	0.62	Slightly significant
30 tuberculoid	7.99	6.2	0.5 to 24.4	0.77	Highly significant
17 other types	5.5	3.6	1.3 to 12.0	0.65	Not significant

The respective means and standard deviations (see Table) were calculated for the leprosy types, of which there were 30 tuberculoid, 21 lepromatous, and 17 maculoanaesthetic or dimorphous. The application of the t-test to their values showed that the significant difference between the means of the two groups was mainly due to the tuberculoid type; this finding is of particular interest in view of the fact of the strong positivity of the lepromin test in tuberculoid leprosy.

Though this study of a representative group of leprosy cases showed a significantly higher blood histamine level than in the group of normal cases, this was as a group, and great variation was found in individual cases. This suggests the value of a linear study of individual examples of the leprosy types in different clinical phases of the disease, such as reaction or quiescence. Ake-Nitzen carried out such a study in cases of chronic urticaria, with illuminating results, for in his cases the histamine content of the blood dropped when the symptoms increased and rose when the cases improved.

Summary

The histamine content of the blood in leprosy subjects as a group has been found to be higher than in non-leprosy subjects. The tuberculoid type showed the more markedly significant higher levels; as in this type the lepromin reaction is strongly positive, the finding is of great interest.

Acknowledgements

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LEPROSY RELIEF AND CONTROL WORK IN TIRUKOILUR TALUK, SOUTH INDIA

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Introduction

Many methods of control have been applied to leprosy, that oldest human disease, but still it remains a great problem in many underdeveloped countries. Ideas about the control of the disease have varied from century to century, but basically leprosy is a rural disease and control methods should be adapted to rural conditions. The aim of this paper is to present and discuss existing control methods of various countries and compare them with Indian methods, in particular with those used in this Centre, which is one of the major control units of the Government of India.

In the past the principles of leprosy control have been greatly influenced by irrational fear of leprosy. Methods tended to be drastic and inhuman, and the previous lack of an effective treatment tended to keep them so. The leprosy sufferer was treated as an outcaste and a danger to society, and was forced to live outside the village, dress differently, and announce himself as "unclean" when any "healthy" individual passed by. This cruel and unscientific attitude was not surprising in view of lack of knowledge of the disease, and it may have been effective in Europe in securing a measure of control. The discovery of the causal organism by Hansen the Norwegian leprologist in 1874 led to some improvement, since leprosy could now be regarded as one of the infectious diseases and potentially controllable. As there was still no known effective therapy, the emphasis on segregation continued, and during the 19th century this was mainly institutional segregation in "settlements". For lack of knowledge there was no effective propaganda to prevent the disease. Then in the latter part of the 19th century leprosy did come to be understood better and the first steps in classification were taken, and Muir enunciated his three principles of control, Propaganda, Treatment, and Survey (P.T.S.) and began to apply them in India. In many countries for some time segregation remained the main bulwark of control.

Modern Consensus of Opinion about Leprosy Control

This has been greatly modified by the coming of effective therapy by the sulphone group of drugs. After leprosy prevalence has been ascertained in a given area, and the environmental conditions studied, treatment facilities can be provided where needed, and we

can start to use the sulphones as a method of control. The new treatment centres are placed carefully wherever needed, so that patients will not have to attend far from their homes. The control action of the sulphone treatment belongs to its power of gradually reducing the bacillary counts, and of late there has been a tendency to make treatment available sooner and more surely by placing the clinics where the patients live, that is, in the villages themselves. Furthermore, domiciliary treatment has been introduced. It has been possible also to improve propaganda because of the growth of our knowledge. Great stress is laid on the protection of children from infection, the importance of early treatment for leprosy, the importance of regularity in treatment, and the need for an enlightened attitude to leprosy.

(One of us, V.E., recently studied leprosy control units, by means of a WHO Fellowship, in Nigeria, Ceylon, Malaya, and Siam, and we propose to describe the working of our Tirokoilur Centre and then compare them with it).

The Tirukoilur Centre

This was established in South Arcot District in April 1955 as a major control unit under the principles of leprosy control enunciated by the Government of India. These principles recognized the anti-bacillary action of the sulphones and the use in control that could be made of it, and set up a number of pilot project areas for the application of intensive mass treatment and simultaneous health education about the infectivity of the disease and its prevention, inculcating a rational outlook on the disease and sympathy between patients and the healthy. It is hoped by this propaganda to overcome the tendency to conceal the disease. Each centre should cover a population between 40,000 and 50,000 in an effort to take the treatment to every patient and contact, if necessary by house to house visits. Two types of centre are proposed. In the Study and Treatment Centre treatment and health education will be joined to leprosy surveys by a special team using laboratory facilities, and trials of BCG will not be forgotten. On the other hand there will also be plain Treatment Centres.

Accordingly the Tirukoilur Centre founded in 1955 comprised four sections, (1) a Treatment Unit with staff of 2 medical officers, 2 nurses, 2 nursing orderlies, 2 compounders, 2 peons, 2 health inspectors, 2 menials; (2) a Survey Unit with staff of 1 health officer, 2 health inspectors, 2 peons; (3) A Laboratory Unit with staff of a pathologist medical officer, 1 technician, 2 menials; (4) an Administrative Unit with 5 clerks. There was a jeep for transport, with one driver. Later some of the staff posts were found to be unnecessary and the staff was reduced slightly.

The *range of work* was based on the former working area of a

non-official leprosy organization called the Thakkar Bapu Kushta Nivaran Sangh. This area is on the north side of the River Penniar in Tirukoilur taluk, and comprises some 80 square miles (about 207 sq. kilom.) containing 54 villages and a total population of 65,290. From the headquarters at Tirukoilur work extends to a maximum of 13 miles (about 22 kilom.) in all directions. Patients obtained from the area were 2,447 (456 lepromatous and 1,991 non-lepromatous) and in addition there were 1,767 patients treated from outside the project area, so the grand total amounted to 4,214. There were 6 outpatient clinics.

In its general plans the Tirukoilur Centre includes a leprosy survey and re-survey at 5 years of all villages in the area, and of some villages outside the area which will serve as controls at a time of evaluation. In the epidemiology attention will be paid to the number of new cases among contacts and non-contacts, any increase in the incidence of leprosy, the progress of patients who have been discharged from treatment, and the effect of migration and immigration on these villages. The main aim is to make treatment available to all patients by means of treatment centres in the villages and house distribution of the sulphones, with adequate records and follow-up. There is a 20 bed hospital attached to headquarters wherein complications and systemic and surgical conditions can be treated. Contacts are observed closely, and laboratory investigations are available at the headquarters laboratory.

The 6 clinics are sited in the zones of the area in such a manner that no patient need walk more than 3 miles to attend. Each clinic functions once a week. The treatment team of doctors, pharmacists, and nursing orderlies travels in a jeep carrying DDS and medicines for intercurrent illnesses, and ointments and dressings. Patients assemble at roadside villages according to a scheduled weekly programme; records are made of treatment and smears and photos taken as indicated. The treatment party thus covers a zone thoroughly and the minor general ailments of the local population are treated as required, which adds to the popularity of the specific campaign. The routine leprosy treatment used is oral DDS, with oral thiosemicarbazone for a few cases who do not tolerate DDS well.

Health Inspectors of the treatment unit have an important part to play. Any absentees are sought out in their homes on the following day by the two health inspectors, who find out the cause of absence and give the sulphones if the cause of absence was reasonable and unavoidable, such as ulceration or the demands of agricultural work. Each health inspector keeps a daily diary of his work which is read daily by the medical officer. Any patient found on these visits to be suffering from complications or an intercurrent disease can be sent to the hospital, which can deal with most of these as well as the surgery for acute neuritis, for gynaecomastia, deformity requiring

amputation, and other conditions. The health inspectors also have the oversight of contacts; they examine healthy contacts every 6 months. Registers are kept of all patients in the area and their contacts. If leprosy is detected in a contact, or any suspicious signs of it, he is sent at once to the medical officer for examination. Still another duty of the health inspectors is to oversee the leprosy patients who have been detected by the survey party and have failed to attend for treatment, and to encourage them to do so. During the regular visits to the villages, the treatment party as well as the health inspector do propaganda to the villagers about the nature of leprosy and how to prevent its spread, with special emphasis on how to protect children.

In the *laboratory* attached to the headquarters of the centre, smears, blood examinations and routine urine and stools examinations are done, but histopathology is not available as yet. The *administrative unit* looks after the office work and records and general matters connected with the centre. The general administration of the centre and the direction of the activities of the sections is in the hands of one of the assistant surgeons who is an experienced leprosy worker.

Discussion of the Working of the Centre

Certain practical advantages emerge in the above method of working. The method of giving treatment to the patients in their homes and villages is a satisfying alternative to the impossible task of providing institutional care for all patients in a heavily endemic area. Because the patients are not extracted from their homes and villages for treatment the problem of rehabilitation is rendered easier; it is a difficult one for institutional patients. The tendency to hide, so common where compulsory segregation is in force, is also counteracted by home treatment, and patients tend to come early in the disease. The cost of maintenance of the patients is saved and the working cost is much less than in the institutional method. There is no disruption of the family structure and social problems do not arise, such as when the patient is the breadwinner; nor is the stigma attached to the disease so noticeable in the home and village scheme as in the case of those segregated in an institution.

Some *difficulties* peculiar to this area have arisen. Most of the people have to work in the fields during the morning and best part of the day, and this hinders attendance. Their poverty also reacts on this, as many cannot afford loss of a day's wages once a week, and many employers are not willing to release them in the mornings which are the best for the field work. Poverty and undernourishment of many involves them in general ailments and in lepra reaction which damage their attendance. Injuries to the limbs from manual labour and field work, and subsequent infection, may afflict some,

and lead on to mutilations. They may not attend hospital because of poverty and lack of transport. As most of the patients are illiterate and superstitious, there are some absences from the clinics because of the influence of various superstitions. In a country where doctors are few and specialist leprosy workers very few, quacks have a great opportunity. They promise quick and miraculous cures and lure many patients from attendance at the clinics. Quacks and a few antisocial persons may decry the prolonged treatment. DDS is available in the open market. A few rich patients occur, but for snobbish reasons fail to attend the clinics, and may take no treatment at all. Even among the poor there are some who reject advice and treatment, knowing that there is no compulsive law about it; this is a cause of worry to the leprosy workers. *An analysis of the reasons for absence* in a token sample of 100 patients, based on the report of the visits of health inspectors over 3 months, reveals the following:—

Agricultural work	169
General ailments and complications ...	38
Temporary migration (to earn a living) ...	65
Negligence (superstitions and ignorance) ...	225
Under treatment by quacks and private doctors	30
Not willing to take treatment at clinics ...	46
	573 visits paid.

Certain *administrative difficulties* are worth reporting. The first is caused by the reluctance of all classes of hospital workers, even doctors, to work in the leprosy field. Those posted to it are usually unwilling workers, and there is no inducement in the shape of extra privileges of pay or leave. The medical officers of the centre are the only people trained in leprosy work so a heavier burden falls on them: they have to conduct the outpatient clinics daily and much of this routine work could be managed by non-medical workers if they were available. The medical officers are few in number and hence the area that can be controlled is limited.

Comparison with Centres Abroad

The senior author recently visited Nigeria, Ceylon, Siam, and Malaya as a WHO Fellow in leprosy control, and is able to report his comparative impressions as follow:—

Nigeria. Leprosy work is now being organized on a mass scale in Northern Nigeria. The one medical officer at headquarters organizes and directs the entire leprosy control work with the help of specially trained non-medical people called leprosy inspectors and dispensary attendants. The local medical officer in each area supervises the dispensary attendants who carry out the routine leprosy treatment. The senior leprosy specialist, formerly the only medical specialist for leprosy (now, in 1958, there is a second) periodically

visits the clinics to assess the progress of the cases and inspect the work of the non-medical personnel. Almost all the rural areas of Northern Nigeria now have leprosy outpatient clinics. It is the senior specialist who trains the dispensary attendants in leprosy work at the various hospitals, and the leprosy inspectors. I visited many of these clinics and found that they are well run. The number of patients treated by this system now reaches the remarkable total of 120,000.

In Eastern Nigeria the control scheme was started many years ago and has had time to show perceptible effect. The special feature is that there is a leprosarium for each province which serves as a focus. The various outpatient clinics studding the province are managed by leprosy inspectors, who again are non-medical personnel who have been specially trained. The medical officers of the leprosarium visit the clinics periodically to watch the progress of the cases and examine the working of the clinics. Thus there is a uniform policy in the province because the leprosarium medical officers share in the central and the district work. Because non-medical personnel do the routine work of the clinics the medical officers are free for the more skilled work and for research. This method would suit India very well.

In Ceylon the incidence of leprosy is low and there are only about 3,000 cases. In Ceylon the special feature is that the care of leprosy patients in an area is the responsibility of the Public Health section of that area. The number of patients being few, individual attention can be paid to them: accurate registry is kept of them.

In Malaya there is no organized leprosy control work apart from a well equipped and first class leprosarium at Kuala Lumpur and another smaller one near Penang.

In Siam there is a huge leprosy problem, as in India, but UNICEF has come to their aid. There is a pilot project at Khon Kaen in Northeast Siam which is a field unit resembling our centre. It works on the same pattern as ours but has non-medical personnel specially trained in leprosy and called sanitarians, who carry on the routine work. The units are of two kinds, stationary and mobile. The stationary units are parts of the respective public health departments and a specially trained public health worker looks after the patients in the area, and domiciliary treatment is included. In the mobile unit there are various teams under charge of the sanitarians who travel to the various outpatient clinics. Here again a few medical officers with the help of non-medical personnel are able to look after the leprosy control work of the whole province. There are several leprosy settlements in Siam but the ideas of leprosy control represented by them have become obsolete. There are interesting "leprosy villages" in the country. I visited one such near Khon Kaen. The WHO officer who founded this village said "Instead of the

patients being forced to stay in settlements which are almost prison camps these villages are ideal. Here many people who have leprosy come and settle down, take treatment from the Leprosy Pilot Project, and at the same time earn their livelihood by engaging in occupations suited to them, such as agriculture, carpentry, and cottage industries." This village is made up of a group of families from various parts of the province. Many stay in the village with their families of children. They are given weekly treatment by the staff of the pilot project. Cultivable lands are made available to them. They seemed quite happy, but I do not recommend this method, for various reasons. There is the same disruption of the social structure as in going to a settlement. They leave their homes, and this would not be popular in India. The control of leprosy by this method has the weakness that children stay with their parents and mix freely with other patients. This is a serious matter, in spite of the fact that preventive DDS is given to the children. Leprosy villages if applied on a mass scale in India would cause endless difficulties over land acquisition in an overpopulated country, and in fact would be impossible. Leprosy villages also add to the financial burden on the state, and the stigma of living in a specified place is similar to that of living in an institution.

Mention should be made of night segregation as advocated by Dr. R. G. Cochrane in India. This was based on the fact that many patients are only in contact with their children during the night, owing to being away on field labour most of the day. Segregation of infectious patients at night would go a long way in the control of the disease. I agree in principle with this method but fear it will not succeed in practice, because considerations of caste and social differences in our villages will hinder it too much.

Conclusion

We have described the methods and ideas of leprosy control current in South India and some other countries visited by the senior author. From our experience as leprosy workers we think the problem of leprosy control can only be solved if it is tackled along with other village problems and not as an isolated entity. Above all the disease can be controlled only if the state, the public, and the patients cooperate with the medical authorities. We reserve for a future date the assessment of the progress of the work of this centre.

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Appendix

(1) Summary of Survey Results in Pilot Project Area:

Number of villages served by the Centre...	54
Population of these villages ...	65,290
Population actually examined	59,149
Total number of leprosy cases detected ...	2,447
(leprom. 456; non-leprom.	1,991)
Average gross incidence of each village	54.66
Average open case rate of each village	17.8

(2) Summary of the Work of the Tirukoilur Centre:

Number of outstation clinics	6
Total number of known cases in the area	2,869
Total number of patients under treatment in pilot area	2,447
(leprom. 456; non-leprom.	1,991)
Number of cases under treatment who originate outside the area	1,767
Grand total	3,870
Number of healthy contacts under observation	10,688
Average number of patients treated at all the six clinics per week	1,656

Results

1955: 1,071 patients on roll at beginning of year.
768 fresh cases registered during the year.
No lapsed cases.
1,839 patients at end of year.
No cases with resolution of lesions.
No lepromatous cases who became negative.

1956: 1,839 cases at beginning of year.
824 fresh cases.
321 lapsed cases or migrated.
2,342 cases at end of year.
59 cases with resolution of lesions.
80 lepromatous cases who became negative.

1957: 2,342 cases at beginning of year.
250 fresh cases.
704 lapsed cases or migrated.
1,888 cases at end of year.
94 cases with resolution of lesions.
72 lepromatous cases who became negative.

ABSTRACTS

On the Nature of the Mitsuda and the Kveim Reaction, **R. Kooij** and **T. Gerritsen,** Dermatologica, Basle, **116**, No. 1, 1958, pp. 1–27.

After a review of the work of previous authors on the lepromin and Kveim reactions, the authors recall that they themselves obtain positive lepromin reactions with normal tissue particles (Int. J. of Leprosy, **24,** 1956, p. 171), and after concentration and centrifugalization of the normal tissue preparations the strength and specificity of the reaction had decreased. This suggested to them the hypothesis that in the Mitsuda reaction the presence of particles and the size of them might be the important factor, and the Mitsuda is in effect a foreign body reaction or isomorphic phenomenon. *In their first experiment* they tested a suspension of particles from normal liver, prepared by the Dharmendra method, against lepromin from lepromatous ear lobes and lepromin from lepromatous liver and spleen, on 10 tuberculoid patients. The preparation from normal liver gave positive results in tuberculoid leprosy, and negative in lepromatous leprosy, and the reactions were similar to those from the lepromins. *In the second experiment* they tested various preparations of normal liver for activity. That obtained by the Mitsuda-Wade method was nearly inactive, but when it was concentrated 12 times the reactivity almost doubled. A Dharmendra preparation from normal liver, 25 times concentrated, resulted in even stronger Mitsuda reactions, and the strongest were obtained with a Dharmendra preparation 100 times concentrated. With the concentrated preparations the lepromatous form of leprosy showed negative results. *In the third experiment* they compared the activity of the 100 times concentrated Dharmendra preparation from normal liver with that of lepromin made by the Mitsuda-Wade method from lepromatous ear lobes, and of another similar lepromin made from lepromatous liver. They found that the preparation derived from normal liver behaved very like the others, though somewhat weaker, but it could be used as a standard preparation. *In their fourth experiment* they studied the importance of the particulate state of the preparation, using bacterial filtrates (Seitz) of (*a*) the Dharmendra preparation from lepromatous earlobes; (*b*) the 25 times concentrated Dharmendra preparation from normal liver; (*c*) a crude preparation from lepromatous liver, obtained by the Mitsuda-Wade method. The results of the average readings showed that the particulate nature is essential for the Mitsuda reaction. *In their fifth experiment* they tested several Kveim antigens on both tuberculoid and lepromatous patients, comparing them with Mitsuda-Wade preparation from normal liver; the results were all very similar. All the Kveim preparations showed weak or negative reactions in lepromatous leprosy and positive results in tuberculoid. In the latter biopsies showed histologically a tuberculoid structure.

The authors conclude that the Kveim antigen does not contain a specific substance and the reaction produced is similar to that of a saline nature. Probably the Kveim reaction differs only quantitatively in healthy people, patients with sarcoidosis, tuberculoid leprosy, and perhaps some other diseases: it is an expression of a sarcoid mode of reaction in certain individuals, and the disease sarcoidosis is a syndrome which can be evoked by many agents. The Mitsuda reaction also seems a sarcoid (tuberculoid) form of foreign body reaction, or an isomorphic phenomenon. It seems to be a general tissue response to foreign bodies, such as leprosy bacilli, normal tissue particles, etc. The tuberculoid or sarcoid mode of reaction may be a general predisposition on the part of certain individuals, and infants and growing children develop it as part of a normal maturation cycle. The absence of the Mitsuda reaction in the lepromatous type may be due to a fault in the reticulo-endothelial system. More study of the Mitsuda reaction and the causes of its absence in the lepromatous may lead us to a better understanding of the pathogenesis of leprosy.

Effect of BGC Vaccination, Lepromin Testing, and Natural Causes in Inducing Reactivity to Lepromin and to Tuberculin. **J. A. Doull, R. S. Guinto, and M. C. Mabalay.** Int. J. of Leprosy, **25,** No. 1, Jan.–Mar. 1957, pp. 13–37.

The authors carried out field work of 7 months in the island of Mactan, Philippines, on a selection of healthy children; there were 550 between the ages of 6 and 35 months. As a control group, an artificial arrangement of 110 sets of 5 children was set up. The inoculations of PPD-S, BCG, lyophilized BCG, diphtheria toxoid, saline, and lepromin were carefully grouped and planned to determine the relative importance of natural causes, initial lepromin testing, and BCG vaccination in producing reactivity to lepromin and to tuberculin. The results tended to show that increase in frequency of reactivity to lepromin in subjects vaccinated with BCG cannot be attributed to the vaccination with BCG alone. Natural causes contribute, and this natural reactivity to lepromin is not necessarily due to infection with *M. leprae.* Infection with *M. tuberculosis* is also an inadequate explanation.

Significance of the Relationship Between the Lepromin and Tuberculin Reactions in Leprosy Contacts. **N. Souza Campos, J. Rosemberg,** and **J. A. Aun.** Int. J. of Leprosy, **25,** No. 1, Jan.–Mar. 1957, pp. 38–48.

They studied children in preventoria and carried out tuberculin and lepromin tests on them. These children had been exposed to leprosy infection, for their parents were leprosy patients. The authors found evidence of the existence of a state of specific resistance or immunity due to the attack by leprosy infection, as well as a state of cross resistance due to tuberculous infection. They analyse the situa-

tion in contacts by distinguishing between those with a state of "leprosy infection" and a state of "leprosy disease." Some contacts are lepromin-positive and have either or both a specific resistance and cross resistance; they may appear to be free of morbidity or show tuberculoid lesions. Other contacts are lacking in resistance and are lepromin-negative; there may be no sign of morbidity or there may be indeterminate or lepromatous lesions. The authors also found that the incidence of leprosy among close contacts is much lighter than suggested by general epidemiological data. They think that priority in care and consideration should be given to lepromin-negative and tuberculin-positive children, and next to lepromin-negative and tuberculin-negative children. They noted a high frequency of positive lepromin reactions in subjects without apparent leprosy, and a high incidence of tuberculoid lesions among the close contacts with open forms of leprosy, and suggest the possibility of the existence of a lymphatic system infection in which clinical signs are absent, and the true onset of leprosy is shown by the visible or detectable clinical manifestations.

Is Erythema Nodosum Leprosum a Favourable Occurrence? **A. R. Davison and R. Kooij.** Int. J. of Leprosy, **25,** No. 2, April–June 1957, pp. 91–98.

The authors incline to the view that e.n.l. is a form of panniculitis and confirm its great increase since sulphone therapy began to be used. They find it is not a reaction to one class of drugs, but is provoked by all drugs which are active against leprosy; yet it is not a reaction to the drug treatment alone, for it does not occur in non-lepromatous cases under any type of treatment. From their study of 200 patients with e.n.l. and 142 without it they derive strong evidence that it is not a favourable sign in the course of leprosy. In the e.n.l. cases the average period of treatment until arrest of the disease was significantly longer, and the bacteriological index much higher and took longer to reach negativity. A mild degree of e.n.l. retarded the arrest of the disease as much as did a severe degree. The incidence of e.n.l. increased with the duration of the disease. The cause of e.n.l. remains obscure: it resembles the Herxheimer reaction, although the attacks last longer and may recur for years. If it is a kind of panniculitis, it is not surprising to find it is an unfavourable reaction which should be controlled.

Chemotherapy of Murine Leprosy. **Y. T. Chang.** Int. J. of Leprosy, **25,** No. 2, April–June 1957, pp. 130–145.

A total of some 25 chemical compounds related to INH have now been studied in tuberculosis by other workers. The most successful in mouse tuberculosis was Compound 337, which is isonicotinyl-hydrazone of 2-carboxymethoxybenzaldehyde, reported on by Siebenmann and Zubrys. A related compound, also with high activity and low toxicity, is Compound 373, which is isonicotinyl-

hydrazone of 2-carboxymethoxy-3-methoxybenzaldehyde. Chang now reports on studies of their effects in mouse leprosy, compared with INH. Compound 337 in continuous administration for 15 months suppressed the infection in the majority of the mice. This is the first drug to do so for so long. Compound 373 and INH were highly active for the 3 months trials, but rather less effective than Compound 377. For all three compounds the suppressive activity over 3 months was not permanent, for when the drug was stopped the disease showed itself again, and caused death.

Effect of X-Ray Irradiation on Excised Earlobe Specimens from Cases of Lepromatous Leprosy. **A. Mukherji.** Int. J. of Leprosy, **25,** No. 2, April–June 1957, pp. 147–149.

Previous work on the application of X-rays to destroy *M. leprae* used high doses for a short time and the result was neither a permanent cure nor any change in the bacteriological picture. Mukherji therefore has used prolonged irradiations in mild doses (63r to 84r over periods of 45 to 60 minutes for 3 to 4 successive days). Smears and histological preparations from pieces of excised lepromatous earlobes thus irradiated showed marked reduction in numbers and beading and disintegration of the leprosy bacilli, and no damage to tissue cells. This suggests practical value as a therapy of local or general lesions.

Patogenia de la Lepra Reacción Lepromatosa (*Pathogenesis of the Lepromatous Lepra Reaction*) **A. J. Melamed.** Leprología, Buenos Aires, **1,** No. 2, July–Dec. 1956, pp. 167–173.

The author's thinking centres round the concept of the lepromatous lepra reaction as a manifestation of sensitivity on the part of the lepromatous tissues which places it in the group of fixed vascular reactions, which also includes periarteritis nodosa. There is clinical and experimental evidence for this. When lepromatous tissue is conditioned or ready to react it is in a state of critical equilibrium with regard to the corticosteroids or conditions such as are brought about by them. Thus every stress factor, such as would increase the consumption of the corticosteroids in the body, would provoke or increase the lepra reaction. It follows that preventive treatment of lepra reaction is preferably directed to removing stress factors and to protecting lepromatous tissue by small continuous dosage of glucocorticoids and other medicaments of similar action.

Mecanismo de la Actividad Antileprotica de las Sulfonas (*Mechanism of the anti-leprosy action of the sulphones*). **M. Bergel,** Leprología, Buenos Aires, **1,** No. 2, 1956, pp. 156–166.

The author reviews the classification and pharmacology of the sulphones used against leprosy, and describes experiments which show the anti-oxidant action of DDS *in vitro* and *in vivo*. He interprets the anti-leprosy action of the sulphones as an anti-oxidant action conferred on them by their amines which stabilize the fats of

the body. In his experiments the addition of 2 in 1,000 of DDS to a diet low in Vitamin E content and containing 15% by weight of linseed oil prevented in rats the peroxidation and polymerization of the subcutaneous fat, as well as of the peri-renal and perigonadal, whereas it took place in the control animals and produced "yellow fat". DDS in the digestive tract averts the oxidation of the small amounts of Vitamin E used in the experimental diets and thus also averts the peroxidative process: also DDS is absorbed and deposited in the fatty tissues and acts as a biological anti-oxidant, replacing the biological activity of the tocopherols in their anti-oxidant capacity. DDS and related compounds (e.g. DDSO) owe their chemotherapeutic value against leprosy to the primary and direct action of their amines which confer this anti-oxidant action, which augments the stability of the lipids of the body. This makes them non-specific agents, for the action is not on the bacilli but on the tissues of the body. By contrast the sulphonamides have a direct antibacterial action on cocci.

Reaction States in Leprosy. **R. Chaussinand,** "Prophylaxie et Thérapeutique de la Lèpre", published by Bibliotheque de Thérapeutique Médicale, Paris, 1958. pp. 66–70.

The subject of reaction states is one of the sections of this booklet by Chaussinand. He thinks that reaction in leprosy probably is provoked by a sensitization of the body to disintegration products of the leprosy bacillus. Tuberculoid leprosy is allergic in nature, and here the sensitization seems to augment the natural resistance and to lead in the end to improvement in the skin lesions, though often enough to an increase in nerve damage. True reaction states do not occur in indeterminate leprosy, but in the anergic lepromatous type the reaction is the most violent, with fever, cachexia, arthalgia, neuritis, ocular lesions, and an increase in cutaneous and mucous lesions. It may even be fatal in the lepromatous if the reaction is long lasting or recurrent. Large doses of sulphones or a too rapid increase in dosage may unchain the reaction. There have been many treatments advised for the control of the condition but none is constantly effective. The author describes many of these and at the present time finds the most effective are *Hydrocortancyl* and *Anthiomaline*. The former is a synthetic steroid, delta-1-dihydrocortisone which has very strong anti-inflammatory and anti-allergic properties. He begins with an oral dose of 30 mgm. and keeps this up for a week or more at need. The sulphone therapy can also be kept going on a slightly less dose, and there should be a low salt diet. The treatment can be repeated in case of relapse. In those cases with repeated reactions one can lead off with Hydrocortancyl and follow with a series of Anthiomaline injections. Anthiomaline is given by intramuscular injections in increasing doses of 6 to 24 cg. per injection three times a week for 3 to 4 weeks.

Fator "N" de resistência à lepra relações com a reatividade lepromínica e tuberculínica: valor dudivoso do BCG na imunização anti-leprosa (*The "N" factor of resistance to leprosy and its relation to the reactivity to the lepromin and tuberculin tests: the doubtful value of BCG in immunization against leprosy*). **A. Rotberg.** Revista Brasil. de Leprol. **25**, 2, April–June 1957, pp. 85–106.

In 1937 the author first suggested the possible existence of a specific factor "N" which governs the resistance to leprosy, and in this paper he marshals the observations of other workers and his own, and the reasoning from them, which lead to a strengthening of the belief in the existence of this factor. He starts from the assumption that a positive lepromin test (LT) indicates a resistance to leprosy, and this is generally agreed. Most children are negative to the LT but later spontaneously become positive. There is no known factor behind this change in reactivity: the small fraction of adults who remain negative to the LT constitute an "anergic fringe" and cannot be distinguished from the positive majority except by the result of the LT itself. Child contacts may show differences in reactivity. It all points to the existence of a constitutional factor which governs essentially the individual capacity to react specifically to the leprosy bacillus. In epidemiology and prevention of leprosy the "anergic fringe" has great practical importance, for this group gives rise to the lepromatous cases. Under the impact of secondary factors, such as debilitating and other unknown conditions, the anergic leprosy-infected individual may change into an active case of lepromatous leprosy.

The author then reviews the immunological relationship between leprosy and tuberculosis. (1) He thinks that tuberculous infection or disease alone will not produce a positive LT without the influence of "Factor N". This is the real reason why lepromatous cases, all practically negative to LT, are yet 50 to 80% positive to tuberculin. There are always some individuals who remain lepromin-negative despite active tuberculosis or tuberculin sensitivity, and they form a narrow fringe of much the same size as the "anergic fringe" referred to above. Therefore the author disagrees with the idea that tuberculosis contributes to the limitation of the endemic of leprosy. On the contrary he thinks it may become one of the secondary factors capable of aggravating an existing leprosy or setting off a latent one. (2) Neither can BCG interfere with the "anergic fringe". In some healthy subjects or active or involuted lepromatous cases lacking "Factor N" it does not produce positivity of the LT. (3) But when the specific "Factor N" is present, leprosy, tuberculosis, BCG, and some other possible factors often produce lepromin-positivity. This would explain the positive LT in non-leprosy areas, and the conversion in children of a percentage of negative LT to positive by BCG.

In this case the BCG artificially and precociously converts the lepromin status of individuals who possess the "Factor N" and who would become lepromin-positive spontaneously in the natural course of events. This anticipation of reactivity might have a clinical value in later leprosy but in prevention and control of the disease BCG is of importance only if it really reduces "anergic fringe", as shown by producing 2 and 3 plus LT in a significantly higher percentage of individuals as compared with the spontaneous lepromin conversion.

Lepromin-reaçao em Holandeses radicados ha 2–3 anos no Brasil e sem contacto conhecido com doentes de lepra (*The Lepromin Reaction in Dutch people settled for* 2–3 *years in Brazil and without known contact with leprosy patients*). **L. M. Bechelli, R. Quagliato,** and **S. J. Nassif.** Revista Brasil. de Leprol. **25,** 2, April–June 1957, pp. 107–125.

A group of immigrant Dutch families, mostly farm-workers, gave an opportunity for study of the lepromin reaction in individuals originating in a part of Europe where leprosy is practically extinct. Mantoux and lepromin tests were made in 240 Dutch people and 89 indigenous schoolchildren who were living in the same environment (which are free of known foci of leprosy). In the Dutch the age groups 0 to 9 years had 80% negative to the LT, and age groups 10 to 19 years had 50 to 60% negative. The higher positives of 2 plus and 3 plus were not found between 0 and 9 years, but from 10 to 19 years such were found in 15 to 20%, and up to 40% in the later ages. The Brazilian children had smaller percentages of negative LT, namely 53% for 5 to 9 years and 30% for 10 to 14. When correlating with the tuberculin test it was noted that 70 to 80% lepromin positivity may go along with Mantoux negativity, and the positivity of the Mantoux does not seem to influence the lepromin positivity. The authors think that the positivity of the LT in these Dutch immigrants may be explained by their possession of Rotberg's "N Factor", though in some cases there may be a cross sensitization to the bacillus of tuberculosis.

The Classification of Leprosy in Japan as described by the Council for Leprosy Research, June 18th, 1956, appears in La Lepro, **25,** Oct. 1956 (Selected Articles) pp. 91–96.

Japanese leprologists conferred on the question of standardization of classification and agreed on the following:—

The types of leprosy are two only, Lepromatous (L) and Tuberculoid (T), but the latter has two subtypes, tuberculoid macular (TM) and Tuberculoid neural (TN). Cases which are indeterminate as L or T are classified tentatively as Group A (atypical) and at subsequent repeated examinations efforts are made to take them out of the atypical group and assign them to L or T. The L type is marked by the following features; smears contain many leprosy bacilli and often globi; the skin has a typical thickening and shade

of colour, and eyebrows depilate; the lepromin test is usually negative; lepra cells occur in tissue sections. The L type is stable and does not change to others. Of the T type, the TM subtype has usually negative smears for bacilli, the skin lesions are hyperaemic and elevated (occasionally not elevated), the lepromin test is usually positive, and histologically the lesion shows a lymphocytic and epithelioid cell infiltration and often giant cells, but no lepra cells; the colour of the lesions is often helpful in differentiating from the L type. (There is no mention of the useful clinical indicator provided by symmetry or asymmetry of the localization of the lesions on the body: the former suggests lepromatous). In the TN subtype, sensory or motor nerve disturbances are prominent, and the only skin lesion which is allowed in this subtype is the hypopigmented macule.

Progressive and retrogressive stages (p and r) are recognized for all, and various clinical and laboratory evidence is sought for them; likewise there is a quiescent stage (q). There is a notation devised for extent of lesions, nerve damage, and mutilations.

Infectivity of Non-lepromatous leprosy. **T. N. N. Bhatta Thiripad,** Leprosy in India, **29,** 2, April 1957, pp. 39–43.

The author discusses the question of the possibility of the infectivity of the supposed closed case, and adopts a cautious attitude, pointing out the difficulty of being sure of the non-infectivity of such cases and on the other hand how often the only possible infecting agent seems to be a closed case. He describes two illustrative cases which seemed to derive their infection from a closed case. He thinks that from the point of view of public health and control of leprosy it is safer to consider all cases of leprosy which are active to be possible infecting agents, especially in these days when we possess an effective remedy and can arrest all types.

Treatment of Dermatitis Herpetiformis with DDS, **N. S. Smelov** and **V. A. Laptev,** Vestnik Dermatologii i Venerologii, Moscow, 1958 No. 2, pp. 7 to 11.

The authors treated 13 patients suffering from dermatitis herpetiformis with daily doses of 100–200 mgm. of DDS, in three to four courses of 6 days. They noted that the treatment was effective in controlling the skin lesions and was particularly good in soothing itch, which is so prominent in this disease.

REPORTS

Rajah Sir Charles Brooke Memorial Settlement, Kuching, Sarawak, Annual Report for 1957.

This leprosarium has a visiting medical officer, Dr. T. M. Kraszewski; a superintendent, Mr. H. MacGregor, four hospital assistants, a dispensary attendant and a laboratory attendant; five patients assist in the work. A laboratory technician was loaned from the Pathological Laboratory, Kuching. There were 393 patients at the end of the year. The Chinese group is still the largest single group, with the Dayak second. There were 62 patients discharged throughout the year. The main treatment is by mouth twice weekly and a few receive injections of DDS in oil or aqueous sulphetrone. There were 32 patients who required treatment of the complication of tuberculosis. The leprosarium has received the benefit of an electrical supply.

The Annual Report of the Mission to Lepers, Hong Kong Auxiliary, for 1957 is a booklet of 33 pages with 6 illustrations.

The large number of the distinguished members of the committees and staff of this organization indicates solid interest and support from the community as a whole. The leprosarium at Hay Ling Chau has been a centre of training of medical students and doctors, health workers, and nurses, and many other interested people visit the centre. It has played its part on television and radio propaganda. There were 498 inpatients at the beginning of 1957 and 133 were admitted during the year. The number discharged with negative certificates was 91 and deaths were 6. Of the lepromatous patients, over 50% have shown marked improvement. Dr. Fraser thinks that the right dose of DDS is the smallest that leads to progressive improvement, and he notes rapid response of Borderline patients. Patients who are sensitive to DDS have been treated with thiacetazone and attempt at desensitization is carried out by administration by mouth of a 1% solution of sulphetrone in very slight increase of doses. There has been an X-Ray survey of the bones of the hands and feet of all patients. There has been active surgery, physiotherapy and rehabilitation. Training of dressers and nurses goes on.

Report of the Leprosy Investigation and Treatment Centre, Zaheerabad, Medak District, Andhra Pradesh, for the year 1957–58.

Dr. Jaipal J. Christian (Hon. Supt. Resident) sends the report. He is assisted by the following staff:—Dr. Vijjender J. Christian (Hon. Leprosy Organizing Officer, Resident); Dr. E. B. Christian (Hon. Principal Leprologist, Visiting); Dr. A. Sham Rao (Hon. Leprologist, Visiting); Dr. N. M. Jaisoorya (Hon. Director of Research, Visiting).

Believing that mass treatment would be the most effective way of controlling such a widespread disease as leprosy, the Centre at Zaheerabad was started on the principles of voluntary segregation, modest expenditure and, at least, partial self-support. Thus, twenty-one years ago, without support from the usual channels and dissatisfied with the accepted methods of dealing with leprosy, we launched this rural clinic in an attempt to bring aid to leprosy patients in their own environment. We are proud to report that the work has prospered and that we have remained self-supporting and in the year under review, have worked on a budget of over 30,000 rupees (£2,750).

The Work of the Clinic

During the year, 248 inpatients were treated in this Centre and of these, 109 were discharged for observation or to attend as outpatients. There were 60 supported patients, 30 self-supported and 50 private patients. There was a high proportion of the infectious type and 5% of cases were children, who are admitted even if non-lepromatous. Admissions were also given for ulcers and reactions. We adopted the practice of short term stay of six to nine months even for lepromatous cases and obtained thereby a more rapid turnover of the patients, and the avoidance of too long a separation of the patient from his home and family. In this way, we were able to double the capacity of our Centre. We did not lose sight of such discharged patients as they attended our other control clinics or the nearest Government Outpatient Department for leprosy. Paying patients were retained until the stage of definite clinical improvement (the charge for such patients being 27 rupees—39s. 6d.—per month).

The outpatient section of our Centre dealt with 425 outpatients of whom 275 were discharged. This applies to outpatients who pay 12 rupees (18s. 0d.) per month for their treatment.

Subcentre at Zaheerabad for Propaganda, Survey, and Outpatient Treatment.

This subcentre deals with all patients who cannot afford to pay for their treatment but who pay a nominal sum of 12 Np (2d.) a week. All living more than 5 miles (8 kilom.) from the centre are strictly excluded. Our leprosy survey of the population of the twenty villages within the 5 miles radius produced the following results:—

Total population	28,480
Population examined	26,202
Leprosy cases detected ...	589
Lepromatous cases	196
Non-lepromatous cases ...	402
Total cases treated	368

During the year, 166 patients were treated at the subcentre and 50 were discharged.

A second subcentre was established this year at Chiragpalli, which is 9 miles (14.5 kilom.) from our main Centre, and occupies 10½ acres (4 sq. kilom.) and contains one thatched hut as a treatment building and three more huts for the workers. Each subcentre has three menials and one caretaker who also acts as a propaganda agent. The Chiragpalli Subcentre was inaugurated on 17th November, 1957, by the Collector of Medak District, Sri K. B. Lal. In the 5 mile (8 kilom.) radius of this subcentre, there are 15 villages and a total population of 13,832. The leprosy survey of 13,602 people revealed 221 cases of leprosy, of whom 62 were lepromatous and 153 non-lepromatous; 104 attend for treatment. The Director of the whole Centre visits the villages and makes contact with all the patients, and patients who are holding back can be persuaded to come for their treatment. All cases who suffer from reactions are given temporary admission until the emergency is over and sent again to attend as outpatients.

We plan to establish yet a third subcentre at Koheer Road, which is 10 miles (16 kilom.) from our main Centre. We tender special thanks to Sri K. B. Lal, who took an active interest and secured a grant of the land at Chiragpalli and Koheer Road. We also thank the D.P.O. Sri Mathur, the Deputy Collector, Sri Gopal Kishen Rao and the B.D.O. Sri Badrinarayan for their help and co-operation.

Treatment

(*a*) *Inpatients.* The routine was oral DDS in dosage of 300–450 mgm. weekly, supplemented with injections once a week of aqueous sulphetrone 20%. Those who could not tolerate DDS were given thiosemicarbazone and hydnosulphone in daily doses of 50 to 75 mgm. For all neural and tuberculoid cases intradermal injections of iodized hydnocarpus oil were given. For lepra reactions, intravenous injections every second day were given of potassium antimony tartrate, calcium gluconate, and vitamin C; cortisone and chlorpromazine were used in a few cases.

(*b*) *Outpatients.* As a routine, all patients were given 300 mgm. of DDS along with aqueous sulphetrone and intradermal injections of iodized hydnocarpus oil, and for all reactions chlorpromazine was used in daily doses of 50 mgm. for seven days in combination with intramuscular injections of stibinol 100 (sodium antimony gluconate).

Laboratory: the routine laboratory tests were carried out throughout the year on 1,758 specimens. *Research:* we ontinued the study of the transmission of leprosy in families both in the inpatients and in the outpatients of our subcentres. Our findings

tend to show that a non-lepromatous case does not infect any healthy individual, whether child or adult, and that a lepromatous case often infects a child but rarely infects an adult. We have also studied the effective action or not of indigenous and homoeopathic drugs. Some had promising results and we wish to continue and expand this study. *Farming:* by using modern methods of cultivation, we have been able to raise the productivity of our farming land and increase the livestock. *Diet:* diet as supplied to our patients is based on jawar and rice or wheat with additions of fruit and vegetables, milk powder, and cheese. All patients are expected to cook their own food except the sick. *Clothing and bedding* are given to all the patients, thanks to the generosity of Rani Kumudini Devi Ramdeo Rao. *Children:* more child patients are applying for admission and we are considering founding a separate unit for them. *Future plans:* we intend to carry leprosy relief wider in the region not only by increasing the inpatient accommodation but by opening up many more subcentres for outpatient treatment. We also intend to conduct an intensive house-to-house survey of all the villages within 20 miles radius (32 kilom.).

A Short History of the Leprosy Investigation and Treatment Centre, Zaheerabad, Medak District, Andhra Pradesh from 1935–1958.
Dr. E. B. Christian, Honorary Principal Leprologist.

Introduction

From 1927 to 1935 the author was medical officer of a large Mission leprosarium in Hyderabad State and found that about 1,500 patients came from Bider, Gulberga, and Osmanabad districts, and that these patients could have contributed to their cost of maintenance. From 1935, the author was a partner in the Gopal Clinic run by the late Major M. G. Naidu and met his son, Dr. N. M. Jaisoorya, who placed strong emphasis on the economics of medical and public health problems in India. This led to a joint determination to study and attack the leprosy problem from the village level, and they began work at Zaheerabad. They were stimulated to do this by their dissatisfaction with the accepted methods of therapeutic attack, by their wish to contribute something to the solution of the vast leprosy problem and by their belief that economic factors lay behind any public health problem and any attack on leprosy in particular must be as inexpensive and as self-sufficient as possible by means of full co-operation from the patients themselves. They also believed that the patients were best treated in their own environment.

The Foundation Phase

They opened outpatient clinics at Zaheerabad, Bider, and Chiragpalli, constructing thatched huts for use as clinic buildings and much aided by the village officers of nearby villages. Very soon

there were attendances of 100 patients once a week in each clinic and 75 per cent of these paid a fee of 1 Rupee (1s. 6d.) a month. To provide residential accommodation for infectious patients and those in lepra reaction, an area of 36 acres (242.8 sq. decam.) of land was obtained by donation of Major Naidu, and on this land, patients who applied for admission built their own huts according to a prescribed model. The first patients paid a fee of 2 Rupees (3s.) per month for their treatment and were self-supporting: at the end of the first year, there were 20 inpatients and 30 outpatients. Thereafter, there was an annual increase in admissions and discharges. Up to 1942 there was a retired English nurse who provided her own cottage and gave her services.

Later Phase

More huts, wells, a treatment building became possible due to aid from many sources, including local authorities, and farm work was started. By 1942 the income had risen to Rupees 2,100 (£107 10s. 0d.) from the patients. From 1942–1950 there was the difficulty of rise in cost of living and the fees from patients were increased to 4 Rupees (6s.) per month inpatient and 3 Rupees (4s. 6d.) outpatient. By 1950 the annual income was Rupees 7,220 (£541). During the years 1950–58, the outstanding social workers, Mrs. Vellodi and Mrs. Boga, became interested and the Indian Conference of Social Workers donated 40 cottages, some money, and help in developing farms and livestock. They also gave a maintenance grant to help deal with a rather sudden influx of inpatients, which then reached 120. Then the Government gave a grant of Rupees 6,429 (£482) per annum and a further single grant for one year of Rupees 3,500 (£261). The Ministry of Health gave a grant of Rupees 15,000 (£1,125) for a jeep and laboratory and surgical equipment. In this last period of 1950–58, the total number of patients treated was 1,412 inpatients and 2,430 outpatients, and the total expenditure for the same period was Rupees 187,511 (£14,063). Towards this, the sale of farm products produced Rupees 23,315 (£1,748) and fees from patients Rupees 92,288 (£6,921). In the last year, it has been possible to open two new subcentres, and two more are planned. To ensure a more rapid turnover of patients, residential patients are not kept more than six to nine months. This measure inspires morale and avoids the stagnant air of the conventional leprosarium. They consider that such centres should not be too large, not more than 125 beds, to avoid complexity and top-heaviness and the danger of becoming uneconomic.