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PRINCIPAL CONTENTS

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LEPROSY REVIEW

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Contents

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Editorial

1 PRICE INCREASE OF LEPROSY REVIEW

We repeat for the third and last time the prospective price increase of this Journal.

With much regret it has been found necessary to double the subscription to *Leprosy Review*. This has been due to investigation of the rising costs of printing and it is intended that, in order to cover the cost of production, the price for a single copy of the Journal will be 10/– whereas hitherto only 5/– per copy has been charged. It is hoped that all subscribers will give us their support and pay the new annual subscription which will be raised to £2 *per annum from 1st January, 1966.*

2 Dr J. Sheskin of the Hadassah Medical Organization, Jerusalem, Israel, has kindly sent a paper on 'Further Observations with Thalidomide in Lepra Reaction'. As this subject is of extreme interest, we have requested Dr W. H. Jopling and Dr T. F. Davey, CBE, and Dr Robert L. Smith to give their comments on the matter of the paper. They have kindly done this and their comments are published in this issue (page 186), adjacent to the paper.

3 Dr Miguel Angel González Prendes died in Habana, Cuba, on the 19th of April, 1965. Dr Prendes will always remain very high in our estimation as friend and scientist, and we propose to publish an Obituary in full detail in a future issue.

Lep. Rev. (1965) **36,** 4, 157/159

Confluent Macular Lepromatous Leprosy

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Under the title 'masked lepromatous leprosy', Davey (1942) described the clinical features of a variety of lepromatous leprosy in which confluent macules occupied virtually the whole of the skin, sparing a few areas. The patient, healthy and symptomless, passed for one of the lighter-hued members of society: the widespread uniform hypopigmentation was not apparent until he was completely stripped for examination, when normally pigmented skin was seen to be restricted to the pelvic girdle.

Owing to the interplay of diverse factors (such as the changing pattern of leprosy in Eastern Nigeria, the non-recognition of early macular leprosy, and the diagnostically confusing prevalence of macular mycotic lesions), confluent macular lepromatous leprosy of the type to which Davey (1942) drew attention, now accounts for rather more than 10 per cent of all new cases of lepromatous leprosy diagnosed in Eastern Nigeria. Frequently, the macules are not noticed, or, if noticed, they are not recognized for what they are, and it is only when lepromatous nodules appear that the thoughts of the patient or his family turn to leprosy.

It may therefore be salutary to record the clinical course and features and the bacteriological findings in a series of 13 such patients recently diagnosed in the Research Unit, Uzuakoli. Many other patients with essentially similar clinical manifestations have been studied during the past few months at the other Leprosy Settlements in Eastern Nigeria, viz., Oji River, Abakaliki, Ogoja, Uburu, Itu and Ekpene Obom.

Mode of presentation

Every patient in this series came for diagnosis and treatment because typical lepromatous nodules had recently appeared on the face or ears. (Nodular leprosy arising *de novo* and without macular or other signs is an uncommon presentation among the deeply-pigmented peoples of West Africa). None of the patients complained of any symptoms referable to the skin or peripheral nerves, and all denied any change in skin colouring. They would pass without remark in a crowd of typical Nigerians, who represent a very wide range of skin hue, from light yellow-brown to very dark brown-black.

Clinical features

When the patients stripped completely, it was evident that (apart from the hairy scalp) the only areas of skin in which the pigmentation was unchanged and the fine architecture undisturbed were to be found in the inguinal region, the lumbar region and the axillae. The superficial extent of this normally pigmented skin varied somewhat, but the basic pattern remained. In the most marked instances, it was reduced to a narrow band about an inch wide just above the ilio-inguinal (Poupart's) ligament, passing over the anterior superior iliac spine, and broadening out slightly above the iliac crest to meet the contralateral band in the midline. The limits of the bordering hypopigmented areas were indistinct, and the width of skin between the obviously normal and the definitely hypopigmented might be as great as an inch. The neck skin is sometimes spared.

One source of difficulty was the individual differences in the skin texture and natural depth of skin pigmentation between the buttocks, and the region just above the iliac crests, and superiorly. A similar state of affairs existed in the neighbourhood of the axillae, though here the condition was complicated by the presence of hair, constant perspiration, and frequently by mycotic and bacterial infection of both hair and skin.

There was very slight tactile impairment in the hypopigmented skin, compared with adjacent normal skin; sweating was unaffected, except in the later stages.

Natural history

By observation of the evolution of these macular lesions, it is possible to piece together a typical

history. Scattered small ill-defined macules, very slightly hypopigmented, first appear usually in the skin of the scapular region, sometimes (in the young and the adolescent) following hazy patches or pre-lepromatous macules. Further crops of similar macules may appear on the back, abdomen, chest, limbs and face. At this stage, an irregular hypopigmented mottling in which the normal skin is represented by slender, darker streaks is the only abnormality visible. The macules extend centrifugally until they coalesce, but further pigment loss does not occur.

When the coalescence has proceeded down to the level of the umbilicus and up to the level of the mid-thigh, discrete macules of precisely similar appearance and degree of hypopigmentation may still be distinguished between the limits of the confluent macules and the areas of apparently normal skin. These discrete macules at length also coalesce.

The process, from start to finish may take from three to five years. It may stop at the macular stage, or progress towards the nodular.

Meanwhile, other features of lepromatous leprosy may be developing, till the full characteristic picture is produced. The eyebrows become thinned, especially the outer third or half, and are eventually completely lost. The peripheral nerve trunks become enlarged and tender at the usual sites, usually from about the third or fourth year onwards.

The skin becomes generally thickened, and less mobile than normal; sometimes the cutis is irregularly lumpy and feels bound down in places to the deep fascia. The central part of the face takes on a greasy appearance.

When acute exacerbation ensues, irregular infiltration and aggregations of pinkish or orange papular masses, together with lepromatous nodules, appear indiscriminately on the considerable areas of skin already the seat of the confluent hypopigmented macules. No acute lesions arise in the areas of apparently normal skin.

* * *

The series of 13 patients now reported (12 males and one female, whose ages ranged from 13 to 40), may be considered typical of some scores at all stages studied, the common feature being the existence of a generalized confluent hypopigmentation of the skin, regularly sparing the three regions specified.

Clinical findings

On the first examination, the extent of the area of apparently normal skin varied necessarily from patient to patient, depending on the actual point in the natural history of the condition when the patient came for diagnosis. In some patients, a few discrete macules were still present around the areas of apparently normal skin.

In 12 patients, the peripheral nerves showed some degree of enlargement. The ulnar nerves were affected precociously, and showed greater departures from the normal than the external popliteals or the posterior tibials. Gross enlargement coupled with hardness of the peripheral nerves at the sites of predilection was not found.

In three patients, there was already some symmetrical thinning of the external third of the eyebrows, and in one patient almost complete madarosis.

One patient had experienced an acute exacerbation in the confluent macular lesions just before admission. Sudden swelling and shininess of the helices of the ears brought another for diagnosis.

Atrophy of the pulp of the little fingers was seen in one patient, together with obliteration of the ridge pattern; and grosser wastage of the hypothenar eminence was present in another. One patient had discrete lepromatous lesions deep in the palmar skin. Early bilateral gynaecomastia was noted once.

Thus, all the patients in this series had at least one clinical feature of more advanced lepromatous leprosy, in addition to the widespread confluent macular rash. In another series, the patients came for diagnosis at an earlier stage in the natural history of the disease, corresponding very closely to Davey's (1942) patient.

One patient has initially a skin of lighter hue than the average. He, too, lost pigment in the same situations as his fellows.

Bacteriological findings

Smears taken from the usual eight sites (four from the skin, two from the ear-lobes, and one from each side of the nasal septal mucosa) all contained numerous *Myco. leprae* and globi. The average Bacterial Index (B.I.) for the 13 patients was 3.17 (maximum: 4.0, on Dharmendra's notation); in seven the B.I. was greater than

3.0, and in six greater than 2.0. The average percentage of 'solid rods' (Morphological Index) was 68.

Interest centres around the smears taken from the three areas of apparently normal skin as compared with those from the obviously hypopigmented skin.

In 10 patients, smears from the inguinal region contained bacilli, and in seven of these globi were found.

In all 13 patients, smears from the lumbar region contained bacilli, sometimes very numerous, with globi in all but two.

In 11 patients, bacilli were found in the axillary skin, with globi in seven.

The morphology of the bacilli corresponded to that found in the adjacent hypopigmented skin.

The concentration of bacilli in these three regions was lower than that in the adjacent skin. Both solid rods and degenerate forms tended to disappear earlier from these regions than from the more heavily infected skin.

It is to be noted that the concentration of *Myco. leprae* (including globi) was consistently lower than that found in the skin between the macules at an earlier stage in the natural history of the disease. In the latter case, the concentration of bacilli and of globi, and the proportion of solid rods are usually comparable with results obtained in the adjacent obviously affected skin. The loss of pigment within the macular areas appears not to depend only or directly on the actual presence of lepromatous granuloma in the dermis.

Immunology

The lepromin test, both Fernandez and Mitsuda, was completely negative in all patients.

Histology

Discrete groups of heavily bacillated lepra cells were present in the dermis. The appearances were typical of early lepromatous leprosy.

DISCUSSION

In this series of 13 patients, the confluent lepromatous macules had been unnoticed, and it was only the appearance of some additional feature that brought the patient for diagnosis. In other and more fortunate cases, leprosy has been suspected before the appearance of such features, when the symptomless, coalescent macules have been the only manifestation of the disease.

Various explanations have been offered to account for the sparing of these three areas of skin from the hypopigmentary effect of the lepromatous process: temperature of the epidermis and the dermis, sweating, skin pH, influence of clothing, pressure, apocene secretions, etc. – but none of these factors is common to all three sites.

The clinical and epidemiological importance of confluent macular lepromatous leprosy needs no emphasis. From the standpoint of the individual patient and that of the community, the condition should be recognized and diagnosed and treated before the onset of irreversible nerve damage.

SUMMARY

A series of 13 patients is reported, in whom a generalized hypopigmentation was for some time the only evidence of leprosy, until other indubitable manifestations of lepromatous disease appeared. The hypopigmentation resulted from the confluence of macular areas, which regularly spared the inguinal region, a band of skin in the lumbar region, and the axillae. These areas of apparently normal skin usually harboured *Myco. leprae* and globi, though not in the same concentration as in neighbouring hypopigmented skin.

ACKNOWLEDGEMENT

My thanks are due to Dr S. O. Egwuatu, Chief Medical Officer, Ministry of Health, Eastern Nigeria, for permission to publish this article.

REFERENCE

DAVEY, T. F. (1942). *Leprosy Rev.*, **13**, 3–5.

Lep. Rev. (1965) **36,** 4, 161/162

Bacterial Clearance in Patients with Lepromatous Leprosy not receiving Treatment

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While the search must continue for a drug that possesses potent and rapid bactericidal or bacteriostatic activity in leprosy – a kind of *therapia sterilisans magna* (Ehrlich) – it seems apposite to emphasize one aspect of the problem that may point the way to therapeutic advance, that is, the capacity of the tissues to deal unaided with non-viable *Myco. leprae.*

Some authorities have held that treatment should be continued as long as any acid-fast material can be detected in routine smears, and treatment for life is often advocated for patients who have had lepromatous or borderline leprosy. While we should never throw caution to the winds and by unorthodox advice put both the patient and his entourage at risk, it might be possible to discontinue anti-leprosy treatment when viable *Myco. leprae* are no longer present in the skin or in deep tissue reservoirs.

In the presulphone days, the gradual disappearance of *Myco. leprae* from the skin was sometimes observed. When today leprosy treatment cannot be continued because of persistent exacerbation, psychosis, etc., the elimination of fragmented bacilli may proceed as if treatment were being given. The following case report, drawn from a series of eight patients with lepromatous leprosy in whom non-viable *Myco. leprae* were progressively eliminated when no treatment was being given, may serve as an example.

Case report

The history of a patient at the Ekpene Obom Leprosy Settlement, Qua Iboe Mission, Eastern Nigeria, under the care first of Dr Oswald Mitchell, F.R.C.S.E., and subsequently of Dr E. M. Davis, has been studied recently. Because of persistent psychosis, anti-leprosy treatment was stopped, but fragmented *Myco. leprae* continued to disappear from the eight sites (skin, ear-lobes and nasal mucosa) regularly examined.

The patient was a woman, aged about 40, suffering from severe long-standing lepromatous leprosy, macular and nodular. The main peripheral nerve trunks were enlarged and tender, and neuropathic ulceration was present on the left forefoot. On admission, the Bacterial Index (B.I.) was 3.4 (maximum 4.0, on Dharmendra's notation), and the proportion of solid rods was low, being only 16 per cent. The patient denied all previous treatment.

She was given dapsone, 100 mg. twice weekly initially, increasing to 200 mg. twice weekly. After 18 months' treatment, she experienced a moderately severe psychotic episode, probably attributable to the combined effects of personality predisposition and environment. By this time, the B.I. had fallen to 2.6, the remaining solid rods having disappeared some three months previously from all sites smeared. Dapsone was suppressed.

Psychosis rapidly supervened when dapsone was cautiously given in 25 mg. doses, and the drug was again discontinued. In spite of the absence of all anti-leprosy treatment for 10 months, the B.I. continued to fall. Acid-fast material was no longer present in smears taken from the skin, and those from the ear-lobes and nasal mucosa showed only very degenerate bacilli and scattered collections of acid-fast dust.

When treatment was again resumed with dapsone (25 mg. twice-weekly), clinical and bacteriological progress continued at the same rate and the remaining acid-fast material disappeared from the ear-lobes and septal mucosa in the course of the next eight months. Treatment thereupon had again to be suppressed by reason of psychosis, but all smears have since remained consistently negative.

DISCUSSION

The rate of disappearance of degenerate and non-viable forms of *Myco. leprae* appears to de-

pend on some factor or factors other than the bactericidal or bacteriostatic activity of a drug. It apparently cannot be increased beyond a certain norm for the individual. Dapsone, thiambutosine, ditophal, B 663 and some other drugs can be shown to ensure a roughly comparable speed of reduction in the proportion of 'solid rods' (or viable forms of *Myco. leprae*), but the time taken for the removal of the last vestiges of acid-fast material from the tissues is variably protracted, and during this time the patient is subject to the risk of tissue sensitivity phenomena.

While some workers go so far as to insist on a positive Mitsuda reaction before considering that a patient who has had lepromatous leprosy can be allowed to return to the community, in our experience the lepromin test remains negative after clinical arrest and when all acid-fast material has disappeared from the skin and nasal mucosa.

Examination of tissue removed by needle biopsy from deep organs (e.g. liver) may furnish evidence of the persistence of viable *Myco. leprae* when they have long since disappeared from superficial sites, but this procedure is not generally practicable.

It is hoped that the recording of this representative history, may stimulate the reporting of other instances in which bacterial clearance of fragmented *Myco. leprae* has proceeded satisfactorily in the absence of anti-leprosy treatment. It may one day be possible to determine in what circumstances it would be justifiable to withhold treatment in patients suffering from tissue reaction to mycobacterial breakdown products rather than from infection with viable and multiplying *Myco. leprae*.

SUMMARY

The progressive disappearance from the skin and nasal mucosa of non-viable *Myco. leprae* in a patient suffering from lepromatous leprosy but not receiving anti-leprosy treatment is recorded. Dapsone was stopped because of severe recurrent psychosis, but clinical and bacteriological improvement continued as when the patient was receiving anti-leprosy drugs.

ACKNOWLEDGEMENTS

My grateful thanks are due to Dr E. M. Davis for calling my attention to this patient, and to Dr S. O. Egwuatu, Chief Medical Officer, Ministry of Health, Eastern Nigeria, for permission to publish this article.

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An Attempt to Stimulate and Depress the Functional Activity of the Inflammatory Cells from Lesions Experimentally Induced by *M. Leprae* and *M. Lepraemurium*

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The tissue macrophages of not previously sensitisized guinea pigs are able to lyse *M. leprae* and *M. lepraermurium* already phagocytised by them (Hadler, 1953a); after the lysis takes place they give origin to epithelioid cells. The rate of mycobacterial lysis performed by the tissue macrophages increases as a consequence of previous sensitization (Hadler, 1953b, 1955). The rat tissue macrophages, on the other hand, are unable to lyse the phagocytised mycobacteria either previously or after sensitization (Hadler, 1953a; Hadler and Ziti, 1955). They store the bacilli within the cytoplasm and transform themselves into lepra cells.

It was stated (Hadler, 1959) that the injection of electro-negative colloidal particles together with either *M. leprae* or *M. lepraemurium* stimulates some functional activities of the macrophages from rat leprosy lesions. There was, as a consequence of the additional effect of the colloidal particles, much evidence supporting the view that the mycobacteria could be readily lysed by the rat tissue macrophages, which further undergo transformation into epithelioid-like cells. Regarding the guinea pig and the rabbit lesions, as a result of the additional effect of the electro-negative colloidal particles, there is a slight decrease of the mycobacterial, rate of lysis, accomplished by the macrophages, and therefore a slower rate of evolution of the leprosy lesions takes place.

These findings are interpreted as a stimulant effect of the colloidal particles on the rat macrophage and an opposite effect on the guinea pig and rabbit macrophages. They suggest, otherwise the possibility that the functional activity of the inflammatory macrophage might be experimentally changed.

On the basis of these statements, an attempt was made to stimulate and depress the inflammatory cells experimentally produced by mycobacterial inoculation, with the aid of substances already proved to have successful action on the inflammatory reaction. Two kinds of substances have been used for this purpose: corticoid hormones and antihistaminic drugs.

Several steroid hormones from the adre cortex are able to influence the inflammatory reaction (Menkin, 1940, 1942, 1951, 1953; Selye, 1949a; Kass and Finland, 1953). Some of them, such as cortisone, exert an inhibitory effect (Hench and col., 1949; Thorn and col., 1950; Woods and Wood, 1950, 1952; Osgood and Favour, 1951; Michael and Whorthon, 1951; Spain and col., 1952; Taubenhaus, 1953), whereas another one, namely desoxycorticosterone, produces an opposite effect, increasing the

*This study was supported by a research grant (E-3760) from the U.S. Department of Health, Education and Welfare of the National Institute of Allergy and Infectious Diseases.

inflammatory reaction (Selye, 1949; Taubenhaus and col., 1951; Rindal, 1953; Taubenhaus, 1953). Hormones from the former group were effective in decreasing the rate of evolution of lesions induced by the *M. lepraemurium* (Nagib and Robinson, 1956; Takayama, 1957; Buttle and col., 1958).

On the other hand, antihistaminic drugs, besides the inhibitory effect on the acute inflammatory reaction (Halpern, 1953), decrease the functional activity accomplished by the inflammatory cells (Jancso, 1947; Kátó, 1956; Kátó and Gözsy, 1956a; Gözsy and Kátó, 1956). As a consequence, they enhance the rate of evolution of experimental tuberculosis (Gözsy and Kátó, 1955) and inhibit the natural defence mechanism of guinea pigs against *M. lepraemurium* (Kátó, 1957).

TABLE I

Experimental animals and treatments. The animals were inoculated with *M. leprae* and *M. lepraemurium* at a same time, except those concerning with the groups 10, 11, 12 and 13, which have received only the latter mycobacterial species

			INOCULUM		TREATMENT OF THE ANIMALS AFTER INOCULATION				
Group	*Animal species*	*No. of animals*	*Dose (mg)*	*Route*	*Treatment previous to inoculation*	*Drug*	*Dose (mg) (*)*	*Route*	*No. of injections throughout the experiment*
1	rat	20	2.0	SC (**)	98°C–1h	DCA	1.0	site	at the 1st day
2	rat	20	2.0	SC (**)	98°C–1h	DCA	1.0	site	at the 1st, 12th and the 24th day
3	rat	20	2.0	SC (**)	98°C–1h	DCA	1.2	p	daily
4	rat	20	2.0	SC (**)	98°C–1h	–	–	–	– (control)
5	rat	20	2.0	SC (**)	98°C–1h	peanut	1 ml	site	at the 1st, 12th and the 24th day
6	rat	15	1.0	ic	4°C–6mon	DCA	1.0	site	at the 1st day
7	rat	15	1.0	ic	4°C–6mon	DCA	1.0	site	daily from the 7th until the 37th day
8	rat	15	1.0	ic	4°C–6mon	DCA	1.2	p	daily
9	rat	15	1.0	ic	4°C–6mon	–	–	–	– (control)
10	rat	30	5.0	p	–	DCA	2.0	SC	each two days
11	rat	30	5.0	p	–	CORT	2.0	SC	each two days
12	rat	30	5.0	p	–	–	–	–	– (control)
13	rat	30	5.0	p	–	DDS	40.0	oral	daily
14	rat	15	2.0	SC	98°C–1h	CORT	2.0	site	each two days
15	guinea pig	15	2.0	SC (**)	98°C–1h	DCA	1.0	site	at the 1st, 12th and 24th day
16	guinea pig	15	2.0	SC (**)	98°C–1h	CORT	1.0	site	at the 1st day
17	guinea pig	15	2.0	SC (**)	98°C–1h	CORT	1.0	site	at the 1st, 12th and the 24th day
18	guinea pig	15	2.0	SC (**)	98°C–1h	–	–	–	– (control)
19	rat	10	2.0	SC	98°C–1h	–	–	–	– (control)
20	rat	10	2.0	SC	98°C–1h	Cl+Pr	2.0	p	daily
21	guinea pig	15	2.0	SC	98°C–1h	Cl+Pr	2.0	p	daily
22	guinea pig	15	2.0	SC	98°C–1h	Cl	2.0	p	daily
23	guinea pig	15	2.0	SC	98°C–1h	Pr	2.0	p	daily
24	guinea pig	15	2.0	SC	98°C–1h	–	–	–	– (control)

(**) The inoculation was carried on 'granuloma pouch' performed by the SELYE (1953) technique.

(*) Dose for each 100g of body weight.
SC: subcutaneous.
ic: intracutaneous.
p: peritoneal.
site: injection performed on the site of inoculation.

DCA: desoxycorticosterone acetate (peanut oil solution).
CORT: cortisone (water solution).
Cl: chlorpromazine: 10–(–dimethylaminopropyl) 2–chlorophenotiazine.
Pr: prometazine: dimethylamino–2–propil–N–thiodiphenylamine hydrochloride.
DDS: 4, 4′ –diaminediphenysulphone.
peanut: peanut oil.

MATERIAL AND METHODS

Adult guinea pigs and rats of both sexes, weighing respectively 300–350g and 130–200g, were inoculated with *M. leprae* and *M. lepraemurium* suspensions, and prepared by the usual techniques, and rendered free of tissue particles with the aid of the Hanks (1951) technique slightly modified. The route of inoculation, the dose of inoculum and the treatment performed on the bacilli previously to inoculation, are given in Table 1. The dose of the inoculum was determined from the weight of already dried bacilli, derived from a suspension sample. Either killed (98 °C for 1 h and 4 °C for 6 months) or living bacilli were used. The animals injected subcutaneously and intracutaneously have received *M. leprae* at one side and *M. lepraemurium* at the other side.

After inoculation the animals were treated as shown in Table 1. Some of them have received corticosteroid hormones, whereas others have been injected with an antihistaminic drug (prometazine) alone or mixed with a hypometabolic drug (chlorpromazine).

Every two days one or two animals of each group were killed by ether inhalation and the site of inoculation was excised for histological examination. From the animals peritoneally inoculated pieces of liver, spleen, lymph nodes and lungs were excised for histological studies. The histological study was carried out on material fixed in Bouin's fluid, embedded in paraffin and stained by HE., Masson's trichromic, azur II – eosin and the Faraco (1938) modification of Ziehl-Neelsen technique.

From the group 10, 11, 12 and 13, 20 animals were kept until natural death, to provide data for the study of the effect of treatment on the animal survival.

RESULTS

The results were based on histological comparison of the inflammatory cells or the bacillary amount, as between treated and control animals. The control animal lesions will not be described, since they were carefully studied elsewhere (Hadler, 1953; Hadler and Ziti, 1955).

DCA effect – the DCA injection performed into the lesion increases the acute inflammatory reaction induced by *M. leprae* and *M. lepraemurium* either on guinea pigs or on rats. The lesions become larger and always display a central abscess (Figs. 1 and 2), surrounded by the inflammatory tissue, where further a greater connective fibrocytic reaction takes place. The development and the rate of evolution of the lesions are shorter in treated rather than in control animals.

Regarding the guinea pig lesions they remain tuberculoid in type, where the macrophages are able to lyse the phagocytised mycobacteria and to develop into epithelioid cells.

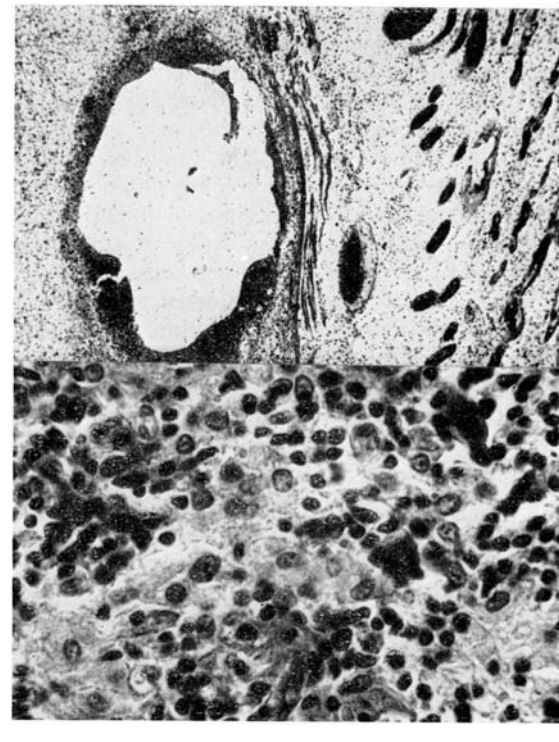


FIG 1 Rat subcutaneously inoculated with *M. lepraemurium* and topically treated with desoxycorticosterone acetate; HE, 50X. Central abcess surrounded by the inflammatory tissue; two days after mycobacterial inoculation.

FIG 2 Rat subcutaneously inoculated with *M. leprae* and topically treated with desoxycorticosterone acetate, Masson's trichromic, 500X. Macrophages showing signs of damage to cytoplasm and nuclei; 10 days after inoculation.

The lesions of treated rats, on the other hand, display some histological changes compared to the control animals. Although most of the lesions are lepromatous in histology, where the macrophages are unable to lyse the phagocytised bacilli and therefore they transform themselves into lepra cells, there are some areas inside the lesions where the structure becomes altered. In these areas the macrophages (Fig. 2) display evidence of cell damage (striking cytoplasmic vacuolization; nuclear pyknosis), and contain only a few bacilli within the cytoplasm. The phagocytised bacilli show striking morphological alterations; they lose their alcohol-acid resistance and become progressively less numerous. Simultaneously, the macrophages transform themselves into epithelioid-like cells, without bacilli within the cytoplasm, suggesting that they are able to lyse the phagocytised bacilli.

The described histological changes only occur in well limited areas of the lesions near the place where DCA was injected and could be better seen when DCA was injected many times on the site of inoculation. The peritoneal injection of DCA was ineffective so far as the histological changes of cutaneous lesions are concerned.

As the DCA treatment was started 7 days after the bacillary inoculation, at a time when the control rat lesions already displayed some lepra cells, an acute inflammatory reaction took place into the lesions. At the same time some lepra cells and macrophages showed signs of cytoplasmic and nuclear damage. Four days later some epithelioid-cells without bacilli inside appeared in the lesion.

The injection of peanut oil alone, does not produce any change concerning the histological structure either of rat or of guinea pig lesions.

Table 2 shows the results concerning the survival of rats inoculated with living *M. lepraemurium* and treated with DCA (group 10 in Table 1). The comparison between the mean of survival of these animals and that concerning the untreated control group, carried on through the analysis of variance, shows no significant differences. Histologically there are no changes in the lesions of treated animals in comparison to the control ones; both show a large amount of active lesions, very rich in bacilli, six months after inoculation.

Cortisone effect – The injection of cortisone either together with the bacilli suspension or into the lesion throughout its development, inhibits the acute inflammatory reaction induced by *M. leprae* and *M. lepraemurium* and decreases the rate of the evolution of the lesion. Such cortisone effect is better seen in the guinea pig lesions.

The lesions of cortisone treated rats are smaller than those of untreated controls and formed by lepra cells, containing a large amount of bacilli within the cytoplasm.

The guinea pig lesions, however, besides longer development and evolution, show some histological changes as an effect of cortisone treatment. The mycobacteria are soon phagocytized by blood leucocytes and tissue macrophages suggesting an increase in the phagocytic activity of these cells. The phagocytized bacilli remain stored within the macrophage cytoplasm for a much longer time than they do in the homo-

TABLE 2

Mean of survival of rats inoculated with *M. lepraemurium*. Effect of cortisone, desoxycorticosterone (DCA) and DDS (4, 4′–diaminodiphenylsulfone) treatment. The DDS treated group provides data concerning the effect of an active drug on the animal survival

	Treatments			*Control*
	Cortisone (*)	DCA (*)	DDS (**)	
Number of animals	20	20	20	20
Mean of survival (days)	228.3±3.5	229.5±4.0	383.0±9.2	237.4±3.9

(*) Treatment started at the first day after inoculation.

(**) Treatment started at the 7th day after inoculation.

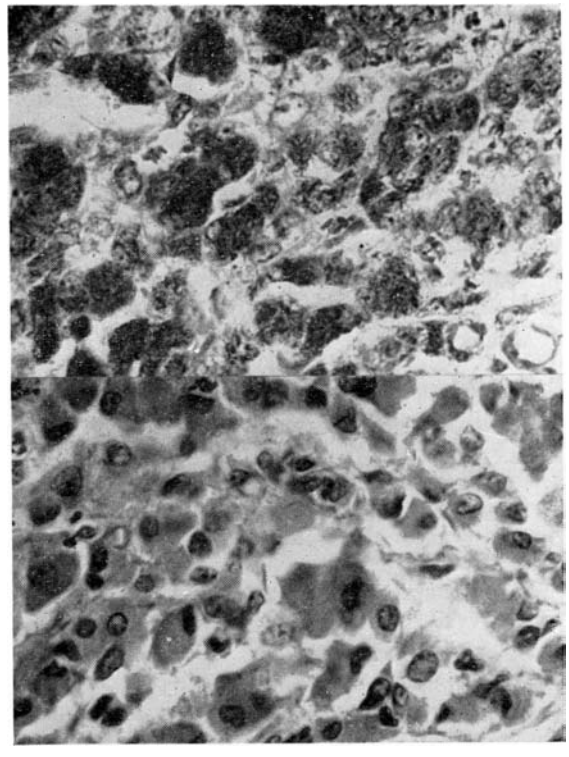
logous cells of control lesions. On the other hand, there is no macrophage damage in the greater part of treated lesions, in spite of the large amount of bacilli within the cytoplasm. Further, two different modes of behaviour of the containing bacillary macrophage could be seen: (a) the bacilli remain stored within the cytoplasm of the macrophage and the cell becomes morphologically similar to the lepra cell, containing a large amount of bacilli and arranged as in leprosy histology; (b) the bacilli are lysed by the macrophage that further undergoes transformation into the epithelioid cell, without bacilli within its cytoplasm. The former macrophage behaviour is more frequently found near the central abcess, at a place where cortisone was injected; the latter were seen in lesion areas far from the abscess, suggesting some correlation between concentration and cortisone effect.

In the lesion areas where the bacillary lysis seems to occur there is cytological evidence of macrophage damage and the mycobacteria show deep morphological alterations.

The cortisone treatment performed subcutaneously on rats peritoneally inoculated with living *M. lepraemurium* does not show any effect on animal survival (Table 2). Furthermore histologically the leprosy lesions of treated animals do not differ from those of control ones.

Chlorpromazine and prometazine effect – This effect is similar to that of cortisone. It appears as an inhibition of the acute inflammatory reaction mainly found in guinea pig lesions. Moreover, the rat treated lesions are also smaller than the control. They are formed by lepra cells, arranged as a lepromatous structure, like the control lesions.

The rate of evolution of treated guinea pig lesions is slower than those of the controls. In the former lesions, the inoculated mycobacteria are sooner phagocytised by macrophages, but remain stored within the cytoplasm, without any evidence of bacillary lysis and of cell damage, in the greater part of the lesion. The bacilli-laden macrophages transform themselves into lepra-like cells (Figs. 3 and 4), containing a large amount of well preserved bacilli. These cells are arranged as a lepromatous-like structure. Only in very limited lesion areas are there morphologi-



FIGS. 3 and 4 Guinea pig subcutaneously inoculated with *M. lepraemurium* treated by chlorpromazine-prometazine; 560X. Lepra-like cells stained by HE and by Ziehl-Neelsen, showing a great amount of bacilli within its cytoplasm; 20 days after inoculation.

cal evidences of mycobacterial lyses and of macrophage damage, until the 30th day of the lesion evolution, in contrast with what happens in the lesions of control animals, where evidences of bacillary lysis can be seen sooner.

The findings concerning the effect of either chlorpromazine or prometazine injected alone support the view that both are active. Nevertheless, it appears that these two substances used together seem to be more effective at an equal dose (interaction).

DISCUSSION

Two distinct and opposite effects could be established with the substances used by us: (1) an increase of the acute inflammatory reaction followed by a functional stimulation of the tissue

macrophages, elicited by desoxycorticosterone acetate; (2) a decrease of the acute inflammatory reaction followed by a partial inhibition of the activity of the tissue macrophages, as a consequence of cortisone and chlorpromazine plus prometazine treatment.

The first effect could be well observed in rat lesions, where some macrophages seems to acquire, as a consequence of the treatment, the ability to lyse the phagocytised mycobacteria. As a result, the histological structure of the lesions is affected and some tuberculoid-like areas containing epithelioid-like cells do occur. The lysis of bacilli seems to act in parallel with the macrophage damage, supporting the view that DCA treatment enhances the bacilli-macrophage interaction.

On the other hand, the second effect was better seen in the guinea pig lesions, where a partial inhibition of the macrophage activity is responsible for the decrease of the mycobacterial rate of lysis. As a consequence the macrophages store a great amount of bacilli and become morphologically similar to the lepra cells.

Both effects show that the two main structural types of leprosy lesions might be affected by drugs.

Several results concerned with the effect of corticosteroid hormones on inflammatory lesions support our interpretation. Cortisone appears to accomplish their effect on the inflammatory cells by inhibiting its physiological activity (Menkin, 1953a; 1953b). As a consequence, although the actual rate at which the *M. tuberculosis* is phagocytosed by the macrophages remains normal after treatment, the number of mycobacteria within each cell is greater than normal, since the digestive capacity of the macrophages decreases (Kass and col. 1953; Lurie, 1955; Lurie and Zapparodi, 1955). This effect is responsible for the latter appearance of the epitheliod cell, as we have observed in the lesions of guinea pigs inoculated with *M. leprae* and *M. lepraemurium* and treated by cortisone. This effect seems to depend upon the action of cortisone that decreases the cellular metabolism and further the cellular activities (Kass and Finland, 1953).

Nevertheless, cortisone acts by increasing the rate of evolution of the rat tuberculosis, the disease becoming therefore able to kill the animals so treated (Michael and col., 1950). Concerning the murine leprosy, our findings show that cortisone does not modify the rate of evolution of the disease. This result suggests that the general defence mechanism against *M. lepraemurium* is not effected by cortisone treatment, in contrast to what happens with *M. tuberculosis*.

It was pointed out that the phagocytoses of *M. lepraemurium* by tissue macrophages either of rats or of guinea pigs is not influenced by antihistaminic drugs (Kátó, 1956). This statement is in agreement with our results concerning chlorpromazine-prometazine treatment. Antihistaminic treated guinea pigs display lesions whose histological structure is similar to those of rats (Kátó, 1957); that is also confirmed by our findings. Nevertheless, either the antihistaminic drug prometazine or the chlorpromazine, which is admitted to be effective as if it decreases the cellular metabolism (Laborit and Huquenard, 1952; Decourt, 1955), produce a similar effect. Both seem to be able to inhibit the mycobacterial lysis accomplished by the macrophages, but they would act by different mechanisms.

The cortisone and antihistaminic effects may be correlated, since some adrenal corticoids inhibited the histaminic liberation by the tissues (Ungar, 1944; Halpern, 1953; Ashi, Funaki and Ono, 1955), increasing the amount of antifibrinolysine (Ungar, Damgaard and Hummel, 1951). Such effect would depend upon the decreasing of mycobacteria-host cell interaction which could be considered as very important concerning the enzyme biosynthesis. Some of these enzymes would be responsible for the mycobacterial lyses. We admit that cortisone and chlorpromazine-prometazine treatment inhibits the synthesis of lytic enzymes by the macrophages. Desoxycorticosterone acetate would show an opposite effect, since it seems to increase the mycobacteria-host cell interaction which stimulates the synthesis of lytic enzymes by the macrophages.

Our findings show, otherwise, that the functional activity of some leprosy lesion cells could be experimentally altered, which produces a striking change in the histological structure of the lesions.

SUMMARY

The attempt to produce an experimental change in the functional activity of the macrophages from guinea pig and rat lesions induced by

M. leprae and *M. lepraemurium* was made with the aid of adrenal corticoid hormones, an antihistaminic drug and a substance that is admitted to depress the cell metabolism.

The findings showed that two opposite effects could be traced, such as:

(1) Cortisone and chlorpromazine-prometazine treatment besides a decrease of the acute inflammatory reaction, exert an inhibitory effect upon the activity of the tissue macrophages. As a consequence there is a decrease of mycobacterial rate of lysis by the macrophages which readily become able to store a great amount of bacilli inside their cytoplasm. This effect could be well seen in guinea pig lesions, where cells similar to the lepra cells do appear after treatment, allowing a marked alteration of the histological structure of the lesion. A lepromatous-like structure emerges in guinea pig treated lesions, whereas a tuberculoid structure arises in untreated ones.

(2) Desoxycorticosterone treatment in contrast increases the acute inflammatory reaction and stimulates the tissue macrophages, as could be established in the rat lesions. As a consequence, some rat macrophages become able to lyse the phagocytized mycobacteria, which allows of the development of some areas containing epithelioid-like cells, without bacilli within the cytoplasm.

Both effects show that the two structural kinds of lesions induced by *M. leprae* and *M. lepraemurium* might be affected by treatment that influences the mycobacteria-host cell interaction. This interaction would be related to the biosynthesis of enzymes, some of which have lytic properties concerning the phagocytised mycobacteria.

RESUMO

Tentou-se modificar experimentalmente a atividade funcional dos macrófagos de lesões produzidas em cobaios e ratos, pelo *M. leprae* e pelo *M. lepraemurium*, mediante o emprêgo de corticóides da adrenal, de um antihistamínico e de uma substância que se admite deprimir o metabolismo celular. Os resultados mostraram que dois efeitos opostos foram obtidos:

(1) O tratamento efetuado com cortisona ou com a mistura clorpromazina-prometazina, além de diminuir a reação inflamatória aguda apresenta ação inibidora sôbre a atividade dos macrófagos dos tecidos lesados. Consequentemente, diminui a velocidade de lise das micobactérias pelos macrófagos, os quais tornam-se capazes de armazenar grande número de bacilos no citoplasma. Ésse efeito é melhor observado nas lesões de cobaios, nas quais surgem células semelhantes à célula leprosa, responsáveis por intensas alterações estruturais das lesões. Ocorre estrutura de tipo lepromatoso nas lesões submetidas a tratamento, enquanto que nos animais não tratados as lesões são de tipo tuberculóide.

(2) O tratamento pela desoxicorticosterona, ao contrário, intensifica a reação inflamatória aguda e estimula o macrófago tissural – conforme foi verificado em lesões do rato. Como decorrência, alguns macrófagos do rato tornam-se aptos em lisar as micobactérias fagocitadas, provocando o aprecimento de algumas áreas contendo células semelhantes às epitelióides, isentas de bacilos.

Êsses efeitos mostram que os dois tipos estruturais encontrados nas lesões provocadas pelo *M. leprae* e pelo *M. lepraemurium* podem ser alterados por substâncias que atuam na interação entre as micobactérias e as células do hospedeiro. A referida interação parece responsável pela biosíntese de enzimas, algumas das quais seriam líticas para as micobactérias fagocitadas.

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Some Cytochemical and Cytophysiological Properties of the Cells from Tuberculoid and Lepromatous Lesions *

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The inoculation of *M. leprae* and *M. lepraemurium* into animals develops two types of lesion: (a) lepromatous lesion, that occurs in rats, mice and hamsters (Hadler, 1953; Hadler and Ziti, 1956); (b) Tuberculoid lesion, found in guinea pigs and rabbits (Hadler, 1953). In a previous paper (Hadler, 1953) the histogenesis, the morphology and a few cytochemical properties of the inflammatory cells from these two types of lesions were studied. The results indicated that in the tuberculoid type of lesions the macrophages are able to lyse the phagocytised mycobacteria, becoming transformed, after the bacterial lysis is done, into epithelioid cells, free of bacilli and lipids. On the other hand, in the lepromatous type of lesions the macrophages were unable to lyse the phagocytized mycobacteria, transforming into lepra cells which contain numerous bacilli and lipid droplets within their cytoplasm.

In the present paper an attempt is made to study the cells from lesions induced by *M. leprae* and *M. lepraemurium* inoculated in guinea pigs, rabbits and rats, as far as some cytochemical and cytophysiological properties are concerned. In addition, human lesions of both tuberculoid and lepromatous type were also studied.

MATERIAL AND METHODS

Adult rats, guinea pigs and rabbits of both sex, weighing 140–220g (rats), 310–365g (guinea pigs) and 2.000–2.500 (rabbits) were used.

Suspensions of *M. leprae* and *M. lepraemurium*, prepared by the usual methods and rendered free from tissue particles with the aid of the Hanks (1951) technique slightly modified, were injected intracutaneously or intraperitoneally. The inoculated dose of bacilli was determined by weighing the already dried bacilli from a suspension sample. When the inoculation was performed by intracutaneous route the hair of a 5 cm. skin area was previously shaved.

The animals were grouped according to the mycobacterial species inoculated, the route of inoculation with the additional injection of electro-negative colloidal particles (Table 1). Two kinds of colloidal particles were employed: (a) 1 per cent Prussian blue water 'solution'; (b) 1:2 water diluted Indian ink. The Prussian blue was injected together with bacilli; the Indian Ink was injected either 24 or 48 hours before the animal was killed, except for the rabbits (see Table 1).

TABLE 1

Throughout the experiment, the animals were killed by ether inhalation according to the following schedule: (a) groups 1, 2 and 4: one or two animals daily until the 3rd day and each three days until the 40th day after inoculation; (b) groups 3, 5, 6 and 8: one animal at the 2nd, 5th, 8th, 12th, 15th and 20th day; of the remaining animals of the group, 8 were killed at the 25th, 30th, 35th and 40th day and those ones of group 3 at the 50th, 60th, 70th and 90th day.

Humans lesions from four lepromatous and four tuberculoid leprosy cases were also studied. In addition, the site of inoculation of the lepromin test performed in six positive and six negative contacts, taken up by biopsy, 20 days after the lepromin injection, were included in this study.

The histological study was performed in such a way that always one rat and one guinea pig subjected to the same experimental condition

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TABLE I

Experimental animals, dose of inoculum and route of inoculation

Group	No. of Animals		Inoculum			Colloidal particles
	Rats	Guinea Pigs	Mycobacterial Species	Dose in Mg.	Route of Inoculation	
1	25	25	*M. leprae*	0.5	Intracut.	—
2	25	25	*M. lepraemurium*	1.0	Intracut.	—
3	10	10	*M. leprae*	2.0	Peritoneal	—
4	20	20	*M. lepraemurium*	4.0	Peritoneal	—
5	6	6	*M. leprae*	0.5	Intracut.	—
6	6	6	*M. lepraemurium*	1.0	Intracut.	Prussian blue 0.1 ml Indian ink 0.1 ml (*)
7	6	6	*M. lepraemurium*	4.0	Peritoneal	Prussian blue 0.1 ml Indian ink 1.0 ml (**)
8	Rabbits 10		*M. lepraemurium* *M. leprae*	4.0 0.5	Peritoneal Intracut.	Indian ink 0.3 ml injected together the bacilli

(*) injected into the lesion, 24–48 h before the animal was killed.

(**) injected by peritoneal route, 24–48 h before the animal was killed.

could be compared; the rabbit and the human material were studied in parallel. Pieces of omentum, spleen, liver and lymph nodes, as well as the site of inoculation were taken up and treated as follows:

(1) *General histological techniques:* fixed in Bouin's fluid or in a solution containing 80 per cent ethanol (85 ml), formalin (10 ml) and acetic acid (5 ml); embedded in paraffin and stained by HE, Masson's trichromic and orcein;

(2) Silver methods: (a) reticulum: fixed in a 10 per cent formalin solution, embedded in paraffin and silver stained by Gomori's (1937) technic; or frozen sections, silver stained by the Rio Hortega's (1943) technique; (b) macrophages: fixed in a 15 per cent formalin solution added, 3g of calcium chloride to each 100 ml of solution; frozen sections, stained by a variant of the Rio Hortega (1927) method.

(3) *Mycobacteria:* Faraco's (1938) modification of Ziehl-Neelsen's stain technique;

(4) *Athrocytic activity:* fixed in Bouin, embedded in paraffin and stained by HE, or fixed in formalin-calcium solution, frozen sections and counterstained with carmine.

(5) *Mitochondria:* Fixed in Regaud's fluid for four days, postchromed for eight days and stained by Altman's fucsin-anilin.

(6) *Histochemical techniques:*

(a) *Lipids:* Two procedures were used: fixed in a formalin calcium solution, frozen sections stained by a 60 per cent ethanol saturated solution of Sudan black B; and fixed 24 h in a formalin calcium-cobalt solution, post-chromed for six days and stained by Sudan black B as for McMannus (1946) phosphatide technique.

(b) *Alkaline phosphatase:* Technique of Gomori (1946a); sodium B glycerophosphate as substrate; incubation for 4 h.

(c) *Acid phosphatase:* Technique of Gomori (1950a) modified by Holt (1959); fixed in formalin calcium solution at 4 °C; paraffin embedded in frozen section; substrate sodium B glycerophosphate; incubation for 2 h.

(d) *Lipase:* Technique of Gomori (1953): fixed in ethanol at 4 °C for 12 h and embedded in paraffin; incubation 10 h in between 40, at pH 7.2 (0.05M veronal buffer).

(e) *Basophil and metachromatic substances:* Fixed in Bouin or ethanol-formalin-acetic acid solution, stained in a 1 per cent Toluidine blue solution, at pH 4.5. Ribonuclease test performed with a boiled acid extract of pancreas.

(f) *Periodic acid Shiff reaction:* Fixed in Bouin or ethanol formalin-acetin acid solution; McMannus (1948) technique.

(g) *Feulgen's reaction:* Feulgen and Rossenbeck's (1924) technique.

RESULTS

The guinea pig and rabbit lesions are histologically similar and therefore they will be analysed together. There are no detectable histological and cytochemical differences concerning either the mycobacterial species or the inoculation route, when single animal species are considered.

The macrophage appears as a cell that plays a key role concerning the development and evolution of the leprosy lesions in all animal species studied, since this cell should be well identified. As an attempt to accomplish this purpose besides its morphology we have based its argentophil properties (Figs. 1 and 2), which seem to be very suitable in this connection.

The macrophage originates from a spindle-shaped and slightly argentophil cell whose cytological and cytochemical properties are summarised in Table 2. Cytochemically this cell shows some quantative differences when guinea pig lesions are compared with rat lesions. Either the alkaline or the acid phosphatase activity, quantitatively estimated by the method of Cleland (1950), slightly modified, are higher in the guinea pig spindle-shaped cells rather than in the same cells from the rat lesions. It is known that such a method to estimate phosphatase activity is not suitable for quantitative purpose (Gomori, 1950a, 1950b). However, in our material it proved to be useful since the results were uniform and permit a good comparison either among several cell types in a single animal species or between a same cell type in two animal species. Nevertheless, the results must be considered only as a semi-quantitative approach.

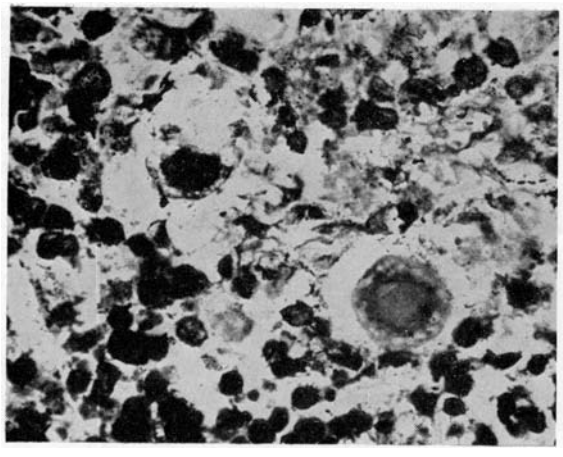
Table 2 shows the main morphological and cytochemical properties of the macrophage. Some quantitative differences could be seen concerning the guinea pig macrophages compared to the rat ones. These differences are cytochemical and cytophysiological in nature. The guinea pig and rabbit macrophages display a higher level of lipase, alkaline and acid phosphatase activity (Figs. 7, 9 and 10); they contain larger amounts of lipid droplets than do the rat macrophages. Although the macrophages in these three animal species are actively phagocytic, those of rat show larger amounts of bacilli inside the cytoplasm. The study of the lesions throughout its development show that the amount of mycobacteria progressively decreases within the guinea pig and rabbit macrophages; in the rat macrophages, on the other hand, the amount of bacilli increases progressively. As the amount of bacilli inside the cell depends upon the ratio between the uptake and the lysis of the phagocytised bacilli, this finding permits two hypotheses: (1) the rat macrophage display a higher degree of phagocytosis; (2) the guinea pig and rabbit macrophages are able to lyse the phagocytised bacilli.

The latter hypothesis is supported by following findings:

(a) The phagocytic activity seems to be similar in the rat and guinea pig macrophages, since both are able to take up Prussian blue and Indian ink particles at a same extent. It is known that athrocytic and phagocytic activity are parallel.

(b) In the rat macrophages the bacilli seldom lie within cytoplasmic vacuoli, and are morphologically normal and stain well; on the other hand in the guinea pig and rabbit macrophages the bacilli lie in cytoplasmic phagosomes, display marked and progressive morphological alterations, lose their alcohol-acid resistance and show some sudanophilia, in contrast with what happens with morphologically normal bacilli.

Furthermore, since the rat macrophages do not show any morphological sign of cell damage, the guinea pig and rabbit macrophages often present cytoplasm vacuolization, degenerative alterations of the nucleus (pyknosis, chromatolysis) and cell necrosis. These findings suggest a more striking integration of bacilli into host cells in these latter animal species.



Silver satining method for argentophil cells; 320X

FIG. 1 Rat intracutaneously inoculated with *M. lepraemurium;* skin lesion. The macrophages appear deep black; the lepra cells are slightly impregnated or unstained; the giant cell shows the central area moderately argentophil.

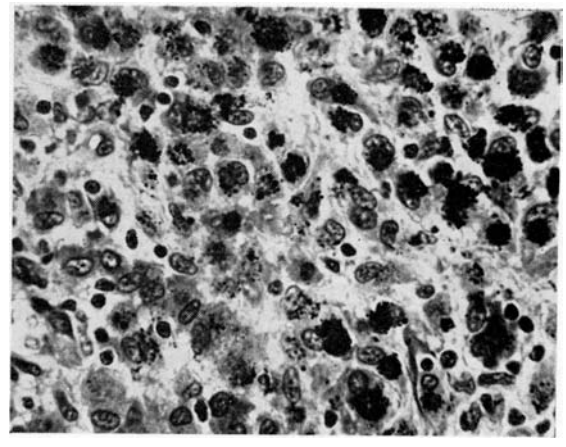


FIG. 3 Rabbit intracutaneously injected with *M. leprae* plus Indian ink; HE stain; 550X. The macrophages (top right) show a great amount of granules within their cytoplasm; the epithelioid cells (centre and left side) contain only a few granules arranged as a circle near the nucleus.

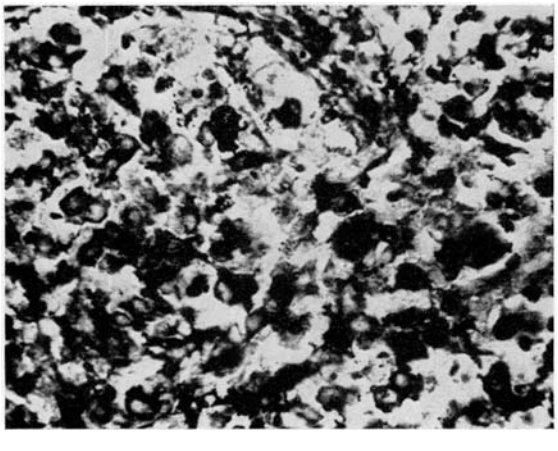


FIG. 2 Guinea pig intracutaneously inoculated with *M. lepraemurium;* skin lesion. The macrophages are strongly argentophil whereas the epithelioid cells are not stained.

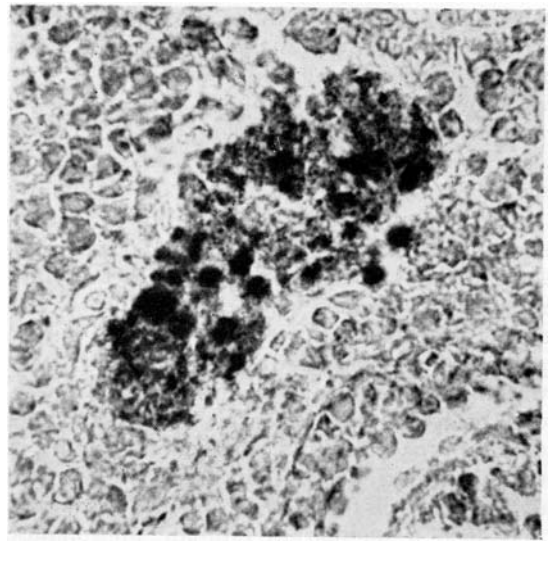


FIG. 4 Rat peritoneally injected with *M. leprae;* lymph node lesion; Sudan black B stained; 300X. The lepra cells contain numerous sudanophil droplets within their cytoplasm.

TABLE 2

Cytological, cytochemical and physiological properties of the main cells found in lesions produced by mycobacteria inoculation into rat and guinea pig tissues

Properties	*Spindle-shaped Cell*		*Macrophage*		*Epithelioid Cell* (*Guinea Pig*)	*Lepra Cell* (*Rat*)
	Guinea Pig	*Rat*	*Guinea Pig*	*Rat*		
Argentophilia	±	±	++++	++++	—	±
Phagocytic activity (*)	±	±	+++	++++	—	++++
Athrocytic activity (**)	±	±	++++	++++	—	+++
Mitochrondria	++++	+++	++++	+++	+++	+
Cell damage	—	—	+++	±	+	—
Sudanophil substances	+	+	+++	+	+	+++
Phospholipids	—	—	+++	±	+	—
Basophil substances (RNA)	+++	+++	++	++	—	—
Metachromatic substances	+	+	±	±	—	—
PAS positive substances	—	—	+	±	—	—
Alkaline phosphatase	++++	+++	+++	++	++	±
Acid phosphatase	++	+	+++	±	+++	—
Lipase	+++	++	+++	±	++	—

(*) Phagocytic activity: estimated on the basis of the amount of bacilli within the cell cytoplasm.

(**) Athrocytic activity: estimated on the basis of the amount of colloidal granules within the cell cytoplasm.

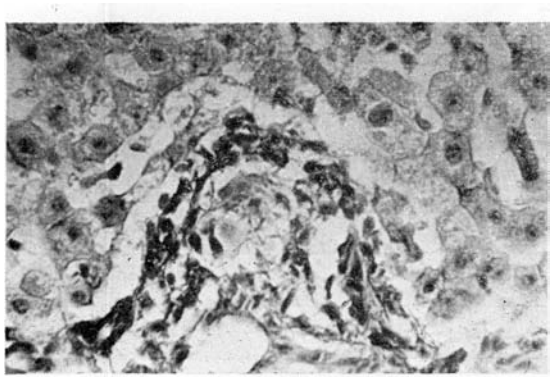
The macrophages become transformed into epithelioid cells in guinea pig and rabbit lesions, and into lepra cells in the rat lesions.

The morphological and cytochemical properties of the epithelioid cells may be seen on Table 2. The morphological study supports the view that epithelioid cells are unable to phagocytise, since they do not contain within their cytoplasm bacilli nor other kind of alcohol-acid resistant substances nor Prussian blue and Indian ink granules. This finding suggests, furthermore, that all detectable substances liberated from the bacilli lysed by the macrophages are soon split off, as the macrophages develop into epithelioid cells.

The lesions from animals that have received bacilli plus Prussian blue or Indian Ink suspensions show much particulate matter within the cytoplasm of the macrophages. As the macrophages transform themselves into epithelioid cells, the granules progressively decrease in size and reduce in number, and when the transformation is accomplished only a few granules lie on a very limited cytoplasmic area (Fig. 3).

There are strong morphological evidences suggesting that Prussian blue and Indian ink particles are slowly digested throughout the macrophage development. The rate of digestion of colloidal particles seems to be slower than the rate of bacillary lysis.

The results obtained by the injection of Indian ink into the lesions, performed 1–2 days before the animals were killed indicate that epithelioid cells do not show any evidence of athrocytic activity.



Alkaline phosphatase activity of the inflammatory cells.

FIG.5 Rat peritoneally inoculated with *M. lepraemurium;* liver lesion; 300X. The lepra cells, which centre the lesion, are very slightly positive. The peripherally situated macrophages show a strongly positive reaction.

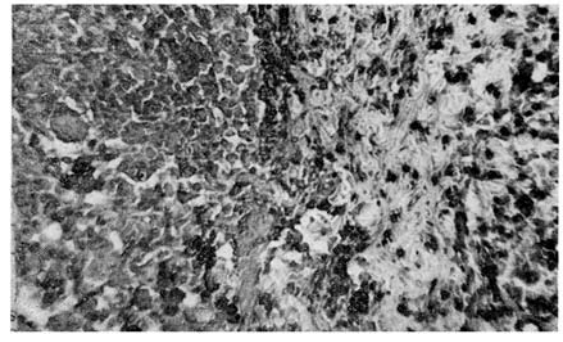


FIG7. Guinea pig peritoneally inoculated with *M. leprae.* Peritoneal lesion; 100X. The macrophages and the blood vessel endothelial cells (right side) are strongly positive. The epithelioid cells and the giant cell (left side) show a lesser degree of positivity.

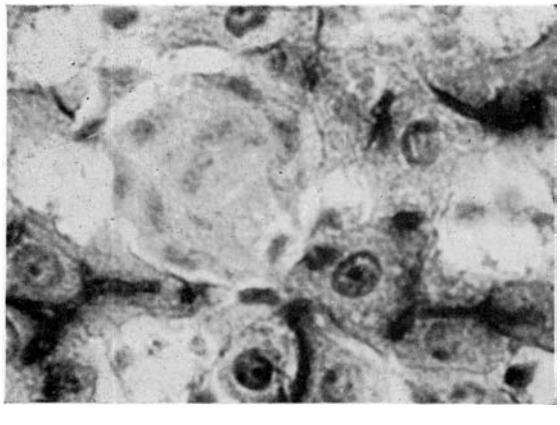
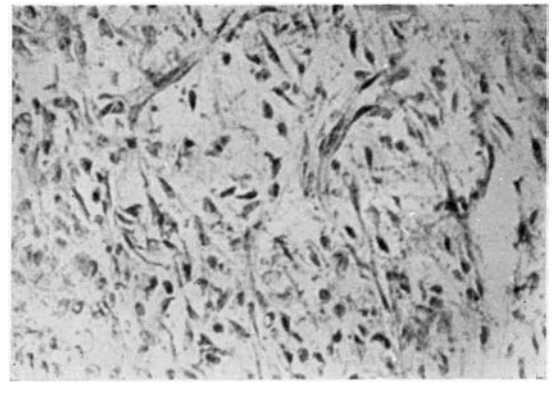


FIG.6 Rat peritoneally inoculated with *M. leprae;* liver lesion, 500X. The lepra cells that constitute the lesion are almost negative.



Acid phosphatase activity of the inflammatory cells.

FIG.8 Rat peritoneally inoculated with *M. lepraemurium;* peritoneal lesion; 300X. The spindle shaped cells and the macrophages, show slightly positive reaction. The lepra cells that centre the lesion, are negative.

The multinucleated giant cells, often found in guinea pig and rabbit lesions, are cytochemically and physiologically similar to epithelioid cells, except concerning its cytoplasmic central area. In this site, on the other hand, the described properties are closely alike to those of the macrophages.

In the rat lesions the macrophages transform themselves into lepra cells, which show many differences, mainly concerned with cytochemical and physiological properties, compared to the epithelioid cells (see Table 2 and Figs. 4, 5, 6 and 8).

The amount of bacilli within the cytoplasm of the lepra cells, although large, increases progressively throughout its development. As the bacilli injected were dead, this result supports the view that the lepra cells are able to phagocytise, in contrast to what happens with the epithelioid cells. The bacilli contained in the lepra cells often do not show morphological alterations at least before the second month of the evolution of the lesion. Only later some alcohol-acid resistant granules do appear. This finding indicates that lepra cells are unable to lyse the phagocytised bacilli, which remain stored within the cytoplasm for a long period. On the other side, the stored bacilli do not seem to produce any harmful effect upon the lepra cells.

When Prussian blue was injected together with bacilli, a large amount of dyed granules appeared scattered within the cytoplasm of the lepra cells, remaining there for a long time. There are no signs, in the most part of the lesions, that could be interpreted as an attempt of the lepra cells to digest the stored granules. Only in some limited sites of the lesions are there evidences of Prussian blue digestion, performed by the macrophages and by cells originated from them; these latter cells show physiological properties which differ from those presented by the true lepra cells (Hadler, 1959).

The lepra cells are able to take up Indian ink particles, injected 1–2 days before the animals were killed. Nevertheless, the athrocytic activity of the lepra cells is at a lower degree compared to that of the macrophages. Only in the retrogressive phase of the leprosy lesions, which takes place two or more months after *M. leprae* inoculation, the lepra cells exhibit a higher degree of athrocytic activity, which becomes similar to that presented by the macrophages.

In the rat lesions some giant cells may be found. Although they are morphologically similar to those found in guinea pig lesions, physiologically and cytochemically they display the same properties as the lepra cells.

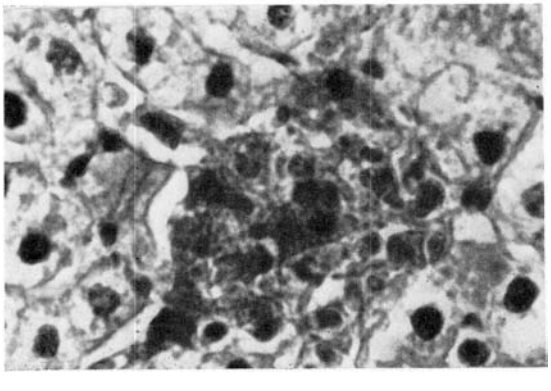


FIG.9 Guinea pig peritoneally inoculated with *M. lepraemurium;* liver lesion; 450X. The epithelioid cells and the macrophages show strong positive reaction.

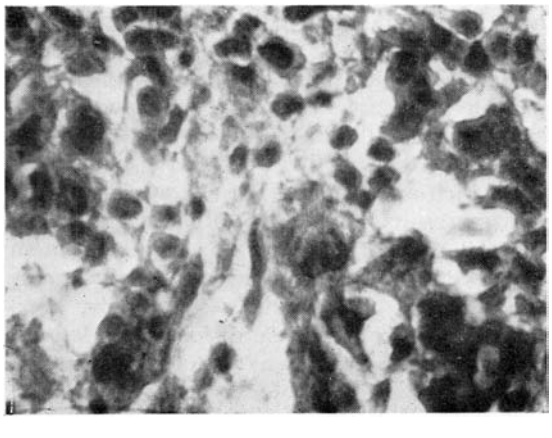


FIG.10 Guinea pig peritoneally inoculated with *M. leprae;* peritoneal lesion; 450X. The macrophages show strong positive reaction; the larger epithelioid cells display a lesser degree of phosphatase activity.

The results obtained with human material (leprosy lesions and the site of lepromin reaction) are very similar to those described above. The macrophage and the lepra cells of human lesions are almost identical to the homologous cells of the rat lesions, either cytochemically or physiologically. On the other hand, the macrophages and the epithelioid cells of human tuberculoid lesions are very similar to the homologous cells of the guinea pig and rabbit lesions.

DISCUSSION

The stated results show that the rat lepra cells are very different cytochemically and physiologically from the guinea pig epitheloid cells. Some quantitative differences are also found when the macrophages of these two animal species are compared.

It appears that the macrophage is the most important cell as far as the histogenesis of lesions produced by mycobacteria is concerned. Therefore, a suitable staining method able to demonstrate this cell was considered as very desirable. Some silver staining techniques have been successfully used to impregnate the inflammation macrophage (Rio Hortega, 1927, 1943; Rio Hortega and Asua, 1921; Marshall, 1946, 1953, 1958), since it is an argentophilic cell (Marshall, 1953, 1958).

The macrophage, therefore, well defined by silver impregnation, was taken as the central point of lesion development. On this basis, the cells that precede and succeed it could be well maintained and studied cytochemically and physiologically.

The lesions induced by *M. tuberculosis* inoculation into guinea pigs show that the macrophages are endowed with alkaline phosphatase activity, in contrast to what happens to the epithelioid cells which are inactive (Russel and col., 1944). Similar results have been obtained in tissue cultures (Weiss and Fawcet, 1953) and in human lesions of the tuberculoid form of leprosy (Klingmüller, 1953). Our results show, however, that either in animal or in human lesions, the epithelioid cells present alkaline phosphatase activity, although in a lesser degree compared to the macrophage. The alkaline phosphatase activity of epithelioid cells is larger than that presented by the lepra cells, which are almost inactive. In agreement with our findings, it has been pointed out that in the experimental rat tuberculosis the 'chronic inflammatory cells' do not show any alkaline phosphatase activity (Grogg and Pearse, 1952a), similar to that which occurs with the rat lepra cell (Klingmüller, 1953).

On the other hand, our results do not agree with those concerned with the acid phosphatase activity of the inflammatory cells. It has been stated that both macrophages and epithelioid cells from tissue cultures (Weiss and Fawcet, 1953) and the 'phagocytes' from rat tuberculous lesions (Grogg and Pearse, 1952a) are provided with a high degree of acid phosphatase activity, in contrast with the guinea pig epithelioid cells which are inactive. Pepler and col. (1958) have found in human leprosy lesions more acid phosphatase activity in lepra cells than in epithelioid cells. It must be considered that it is very difficult to correlate cells defined by different criteria. Furthermore the semi-quantitative approach concerning the acid phosphatase activity performed by us, in a material where the macrophages were accurately recognised by its argentophilia, seems to be more suitable than other methods already used to the same purpose.

Lipolytic enzymes such as stearases (Vogel, 1951) and lipase (Gomori, 1946b; Wotton and col., 1950) have been found in the guinea pig macrophages. On the other hand, the lepra cells do contain many lipid droplets within their cytoplasm (Rath de Souza and Alayon, 1942; Villela and Linhares, 1943; Linhares, 1944; Rath de Souza and Souza Lima, 1950; Azulay and Andrade, 1952; Harada, 1955; Sugai, 1958) and show a feeble lipolytic activity (Emerson and col., 1932), whereas the human epithelioid cells apparently do not contain lipids (Rath de Souza and Alayon, 1942; Rath de Souza and Souza Lima, 1950; Azulay and Andrade, 1952). These results were confirmed by our findings.

Both the guinea pig and the rat macrophage show cytological similarities. Nevertheless, they display several physiological and cytochemical differences, which appear to be correlated with its ability to lyse the phagocytised bacilli Consistent evidences concerning the mycobacterial lyses within the guinea pig and rabbit macrophage are provided by the study of the lesions throughout their development and evolution. Electron microscopic studies performed on

human tuberculoid leprosy lesions support this view (Nishimura, 1960).

There should be some correlation between acid phosphatase activity, the functional role of the macrophage and its transformation into the epithelioid cell. This view is supported by the already admitted effectiveness of this enzyme in splitting off tuberculoid phosphatides (Grogg and Pearse, 1952a; Gerstl and Tennant, 1941). As both alkaline and acid phosphatase as well as lipase appear at a higher level in the cells which are able to lyse the mycobacteria, it would be admitted that the enzymic production capacity by the cells has a great role concerning the bacterial lysis.

On the other hand, the biosyntheses or the activation of enzymes would depend upon the strength of cell stimulation. As the interaction of bacilli and host cells is closer in guinea pig lesions than in rat lesions, the different physiological behaviour of the inflammatory cells in these animal species would be a consequence of the effectiveness of the stimulus. Some experimental results support this hypothesis. Hadler (1959) injecting electro-negative colloidal particles together, either the *M. leprae* or the *M. lepraemurium* in rats, found in limited areas of the lesions striking evidence of mycobacterial lyses performed within the macrophages. These cells further undergo transformation into epithelioid-like cells. This result was interpreted as a consequence of the enhanced stimulation effect of the rat macrophages accomplished by the interaction of the bacilli plus the colloidal particles. Hadler, Ferreira and Ziti (unpublished paper) inoculated guinea pig with *M. leprae* and *M. lepraemurium* and treated them with cortisone and an antihistaminic drug. Their findings show that the treated guinea pig macrophages become unable to lyse the phagocytised mycobacteria, and as a result lepra-like cells do appear in the lesions. In such instance, the treatment performed seems to inhibit the synthesis of the lytic enzymes by the macrophage, at the same time that the interaction of bacilli-host cells decreases. Therefore, by acting on the interaction of bacilli-host cells the functional activity of the inflammatory cells may be experimentally changed.

The different behaviour of guinea pig and rat macrophages when *M. leprae* and *M. lepraemurium* are inoculated appears as a property of their own tissue cells, since it is independent of previous mycobacterial contacts (Hadler, 1953) and it is not modified by experimentally induced either specific or para-specific hypersensitivity (Hadler, 1956; Hadler and Ziti, 1955).

SUMMARY

The lesions induced by *M. leprae* and *M. lepraemurium* inoculation in the guinea pig and rabbit display a tuberculoid structure, whereas in the rat they present a lepromatous structure. A cytochemical and cytophysiological study carried out on these two kind of lesion structures showed many differences concerning the biochemical and the functional activity of the macrophage, which seems to be responsible for the development of physiologically different cells: the epithelioid cell in the tuberculoid structure and the lepra cell in the lepromatous structure. The macrophage was considered as the most important cell concerning the lesion development and therefore was carefully identified, mainly by its argentophilia.

The guinea pig and rabbit macrophages, are able to lyse the phagocytised mycobacteria, and display a high degree of alkaline and acid phosphatase activity. They quickly split off lipids (phospholipids included) within its cytoplasm, since they present a high degree of lipase activity. They show numerous mitochondria and some ribonucleic basophilia in its cytoplasm. The macrophage transforms itself into the epithelioid cell, which is not argentophil, is free of bacilli and contains very few lipids within its cytoplasm. The epithelioid cell displays, furthermore, alkaline and acid phosphatase and lipase activity; it is a cell that does not display phagocytic and athrocytic activity, but it is able to split off the electro-negative colloidal granules already contained in its cytoplasm.

In the rat the argentophil macrophage is unable to lyse the phagocytised mycobacteria, shows a feeble alkaline and acid phosphase activity; splits off very slowly the lipids contained in its cytoplasm, which agrees with its very feeble lipase activity. In this animal species the macrophage transforms itself into the lepra cell, which is slightly argentophil, and contains a great amount of bacilli and of lipid droplets within its cytoplasm. This cell is void of lipase, alkaline and acid phosphatase activity and of ribonucleic basophilia. It is able to phagocytise and to athrocytise granular matter.

The results obtained in human tuberculoid and lepromatous lesions were very similar to those stated before. In the tuberculoid lesions the macrophage and the epithelioid cell are similar to the homologous cells from guinea pig lesions. On the other hand, in the lepromatous lesions the macrophage and the lepra cell are similar to the cells found in the rat lesions.

The different behaviour of the inflammatory cells in these two types of lesions seems to depend upon the interaction of bacilli and host cells, which provides the stimulus concerning the biosynthesis of enzymes; some of them would be accounted for by the mycobacterial lysis. This hypothesis is supported by results concerning the experimental stimulation and inhibition of the inflammatory cells induced by the *M. leprae* and *M. lepraermurium* inoculation.

RESUMO

As lesões induzidas pela inoculação do *M. leprae* e do *M. lepraemurium*, em cobaios e coelhos, apresentam estrutura tuberculóide. No rato estas lesões possuem estrutura lepromatosa. O estudo citoquímico e citofisiológico, efetuado nesses dois tipos de lesões, mostrou diversas differenças concernentes à atividade bioquímica e funcional dos macrófagos, as quais parecem responsáveis pelo aparecimento de células fisiològicamente diferentes: a célula epitelióide na estrutura tuberculóide e a célula leprosa na estrutura lepromatosa. O macrófago foi considerado a célula mais importante no que concerne ao desenvolvimento das lesões e por isso, foi identificado cuidadosamente – principalmente através de sua argentofilia.

Os macrófagos do cobaio e do coelho são capazes de lisar as micobactérias fagocitadas e apresentam forte atividade phosphatásica, tanto alcalina quanto ácida. Eles metabolizam ràpidamente, lípides contidos em seu citoplasma e possuem forte atividade lipásica. Apresentam numerosas mitocôndrias e pequena basofilia ribonuclêica. O macrófago transforma-se na célula epitelióide, que não é argentófila – não possui bacilos e contém poucos lípides no citoplasma; não exerce fagocitose nem atrocitose mas é capaz de metabolizar corantes eletronegativos contidos em seu citoplasma.

No rato, o macrófago argentófilo é incapaz de lisar as micobactérias fagocitadas; apresenta fraca atividade fosfatásica ácida e alcalina; metabolisa muito lentamente lípides contidos em seu citoplasma, o que concorda com sua fraca aftividade lipásica. Nesta espécie animal o macrófago transforma-se na célula leprosa, fracamente argentófila, muito rica em bacilos e em gotículas de lípides. Esta célula é isenta de lipase, de atividade fosfatásica ácida e alcalina e de basofilia ribonuclêica. A célula leprosa é capaz de fagocitar e atrocitar.

Os resultados obtidos em lesões de lepra humana confirmam os verificados em animais. Nas lesões tuberculóides o macrófago e a célula epitelióide são semelhantes às células homólogas presentes nas lesões do cobaio. Ao contrário, nas lesões lepromatosas o macrófago e a célula leprosa se assemelham às células emcontradas nas lesões do rato.

O comportamento diferente das células inflamatórias nesses dois tipos de lesões parecem depender da interação bacilos-células do hospedeiro, a qual produz estímulo responsável pela biosíntese de enzimas, algumas das quais produziriam a lise das micobactérias.

Esta hipótese é apoiada por resultados provenientes da estimulação e da inibição experimentais das células inflamatórias induzidas pela inoculação do *M. leprae* e do *M. lepraemurium*.

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Further Observation with Thalidomide in Lepra Reactions

J. SHESKIN, M.D.*

Thalidomide was recently reported to exert a rapidly beneficial effect in the lepra reactions of lepromatous leprosy patients[1] [2]. This paper reports further experience with this drug over a 10-month period in thirteen patients who suffered from such reactions.

CLINICAL MATERIAL AND METHODS

Twelve of the patients had lepromatous leprosy; one patient had been diagnosed as borderline type. Ten were males and three were females, aged 23 to 54 years. Thalidomide was not given to female patients in whom there was thought to be a possibility of pregnancy occurring.

Most of the patients had been treated for lepra reactions, previous to November 1964, with courses of intramuscular stibophen, 15 to 20 ml., given over a period of five days. If this failed to control the reaction steroids were given, the usual drug being prednisone 20 to 30 mg. per day, often with the addition of intramuscular A.C.T.H. 20 to 60 units per week. In some cases doses of this order had to be maintained for months or even years; attempts to reduce the maintenance dose resulted in recurrences of lepra reaction. Such patients thus developed many of the undesirable effects associated with long-term steroid therapy, and in addition still suffered from reaction from time to time. The frequency of reactions among the 13 patients as a group prior to November 1964 was between once per week and once in two months.

Owing to the limited number of patients surveyed only a simple comparison has been attempted between the response to thalidomide during a lepra reaction with that of a placebo tablet of similar appearance and taste. The tablets were either given alone or together with existing steroid and/or dapsone (diamin-diphenyl-sulphone) therapy. The total number of reactions studied during this period was 22. In three patients only one reaction occurred, whilst 19 reactions occurred in the other ten patients. An account of the treatment of one patient who suffered four reactions since November 1964 illustrates the method employed in trying to assess the efficacy of thalidomide.

In November 1964 a 46-year-old man suffered from a reaction in spite of a maintenance dose of dapsone, 100 mg. per day, prednisone 20 mg. per day and A.C.T.H. 20 units three times a week. When thalidomide (100 mg. every 8 hours) was added to the existing regimen, clinical improvement was noted within 24 hours. After three days both thalidomide and dapsone were stopped, and the steroids gradually withdrawn. In December 1964 a severe reaction followed. There was no spontaneous remission after 48 hours, and treatment with thalidomide (100 mg. 8-hourly) alone was started. The patient responded rapidly, as he had done a month previously. Ten days later when thalidomide was stopped no immediate reaction followed. This patient in the past had always suffered reactions when receiving dapsone without steroids. A week later, therefore, dapsone was reintroduced (100 mg. per day) and ten days later a reaction occurred. The dapsone was continued with the addition of placebo tablets for two days, but without clinical change. Without reducing the dose of dapsone, 100 mg. thalidomide were given three times daily, instead of the placebo. Dramatic improvement was seen within 12 hours. After one month both dapsone and thalidomide therapy were discontinued, and the patient remained without treatment until a further reaction occurred after four weeks. Thalidomide was then given alone. The result was as on the three previous occasions. Since then the patient has continued free from reaction on 400 mg. thalidomide per day

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for three months, and subsequently on 200 mg. per day for three months.

In similar fashion, 22 reactions were treated with 34 assorted therapeutic trials. There were five drug combinations: dapsone plus placebo, placebo alone, dapsone plus prednisone plus thalidomide, dapsone plus thalidomide, and thalidomide alone.

Urinalysis was performed before starting thalidomide treatment, and fortnightly thereafter; as were the following blood examinations: haemoglobin, white blood count, differential count, urea, fasting glucose, cholesterol, albumin/globulin ratio, cephalin flocculations, thymol turbidity, thymol flocculation, bilirubin and alkaline phosphatase.

RESULTS

The clinical response within 48 hours to the five drug variations is shown in the Table I.

In each of 22 tests in which thalidomide was given, either alone or in combination with other drugs, there was rapid clinical improvement, both subjective and objective. There was a fall in temperature and cessation of rigors. The patients slept better, nausea disappeared, and the appetite increased. Muscle, joint, nerve and testicular pains were all relieved, as were headaches. There was resorption of the skin lesions of the lepra reaction and reduction of the size of enlarged limph nodes.

All the patients receiving thalidomide gained weight, in one case from 65 to 73 kg. within five months, and there was some decrease in the erythrocyte sedimentation rate. Changes in histological and bacteriological status, and in the response to lepromin-testing, will be detailed in a later report.

Two of the patients who had had particularly severe reactions (on the average every six weeks for 12 and 22 years) were free from reactions for six months respectively after receiving short courses of thalidomide, while continuing dapsone treatment without interruption. The first of these patients had received two courses of thalidomide in December 1964 (300 mg. daily for 14 days, and 200 mg. daily for three days), and one course in March 1965 (400 mg. daily for six days). The other patient had been given a single course of 400 mg. thalidomide daily for five days in January 1965.

In one patient with severe pains and thickening of the ulnar nerve, there was relief of pain within 24 hours, and by the ninth day of treatment the nerve felt normal but still rather tender. A second patient who had severe polyneuritis also experienced relief of nerve pains within 24 hours, and the affected nerves felt normal after 15 days of treatment, although here again there was tenderness on pressure.

Nine of the patients had active lepromatous lesions which also appear to have improved during the treatment.

In twelve tests the placebo tablet was used: in no case was there any improvement in the patient's condition.

DISCUSSION

Thalidomide was given to 13 unselected patients whose reactions had generally been difficult to control with stibophen or steroids. Thalidomide therapy, in contrast to a placebo, was able to cause a remissions of the signs and symptoms of lepra reaction within 48 hours in all the cases. This improvement occurred whether thalidomide was given alone or together with steroids and/or dapsone. No patient suffered from iritis or iridocyclitis during this period and therefore no evaluation could be made of the effect of thalidomide in these conditions.

Side-effects

In no case was it necessary to stop treatment because of toxic reactions. In three patients there were apparently no side-effects. The other ten patients complained of drowsiness, which was severe in two cases. Constipation, often severe, occurred in nine patients, usually after about three days' treatment. In seven patients this cleared up within two months of treatment, but in two patients the symptom had not yet remitted after nine and six months respectively. During the first month, dryness of the oral and nasal mucous membranes was complained of by seven patients, in two of whom it was still present six months later. Erythema of the face and chest appeared in five patients after about nine days of treatment. Pitting oedema was seen during the first month of treatment. It affected both feet in one patient, and in three patients there was recurrent oedema localised to one foot, one wrist, or one side of the face respectively. Three patients complained of mild

transient difficulty in erection which began after about 2 months of treatment. A fourth patient, a 53 year old childless married man, has been entirely unable to experience erection since the beginning of treatment 7 months ago. In three patients a vesiculobullous eruption occurred within the first week of treatment. This disappeared within one month in two patients and within three months in the third. One patient developed a ravenous appetite, which had not remitted after six months. In a further patient an eczematous rash appeared on the abdomen on the third day and disappeared within one week.

No significant abnormalities were detected in the urine or blood examinations.

The minimum effective daily dose seemed to be 400 mg. in four divided doses. There was no apparent advantage in giving the same total dose in six divided doses. The drug appeared to be less effective when a similar dose (6 mg. per kg. body weight) was given intramuscularly.

Although experience is as yet limited both as regards the number of patients and the period of follow-up examinations, the immediate beneficial effect already shown in patients suffering from lepra reactions was substantiated, and it would seem to indicate that thalidomide may be helpful in the treatment of this type of patients. A study on a larger number of patients, to determine the optimum maintenance dose and the duration of treatment, is now being planned.

SUMMARY

1. Lepra reactions in thirteen cases of lepromatous leprosy responded within 48 hours to treatment with thalidomide. Improvement occurred whether thalidomide was given alone or together with steroids and/or dapsone.

2. A placebo tablet given under similar conditions was ineffective.

3. The dosage used was generally 400 mg. daily given over periods of up to seven months.

4. Toxic effects were numerous, and consisted of drowsiness, constipation, dryness of the oral and nasal mucosae, erythema of face and chest, oedema localised to one extremity, mild difficulties in erection, excessive appetite, vesiculobullous and eczematous rashes. In most cases these effects were transient and in no case was it necessary to withdraw the drug because of the side effects.

5. During the 10-month observation period, no pathological changes were noted on fortnightly examination of urine, peripheral red and white blood cells and liver function tests.

TABLE I

Immediate Effect of 34 Assorted Therapeutic Tests in 22 Lepra Reactions

Treatment	*Number of Therapeutic Tests*	*Clinical Improvement within 48 hours*
Placebo and Dapsone	6	0
Placebo alone	6	0
Thalidomide and Dapsone and prednisone	1	1
Thalidomide and Dapsone	8	8
Thalidomide alone	13	13

ACKNOWLEDGEMENT

Thalidomide was put at our disposal by Taro Pharmaceutical Industries Ltd., Haifa, Israel; and Grunenthal Chemical Industries, Stolberg, W. Germany, for which grateful thanks.

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Comments

The Editor has invited my comments on Dr Sheshkin's paper, which I read with interest.

The care of the patient who is subject to recurrent and severe acute phases can be one of the most difficult problems confronting the leprologist, and one has every sympathy with the concern which prompted Dr Sheshkin's study. At the same time, the choice of thalidomide for a study of this nature is not a little surprising. The appalling results it may have in pregnancy have rightly discredited thalidomide in the mind of the general public, and the publicity surrounding it, and the emotional reaction associated with it, clearly call for the utmost caution in its use in any drug trial. It would be legitimate to ask whether the patients knew what they were receiving, and if so, how far their emotional response may have influenced the findings.

The report of promising results in any form of therapy, no matter how bizarre, is sufficient to stimulate enthusiasts to proceed with its use. Here the author has a considerable responsibility. The risk remains that sooner or later the drug will be administered during pregnancy. In any case, how certain is it that the drug is without danger apart from pregnancy. What for instance is its effect on spermatogenesis, a very cogent matter in the type of male leprosy patients who might be included in future trials. I can find no reassurance on this point in the literature. The more extensive use of the drug could be justified only if results with it in the most difficult cases were of such brilliance as to outweigh its known serious defects. The results published in this paper do not match up to such a standard. The number of patients is too few for much store to be placed on the clinical remissions recorded after its use. The history of leprosy is strewn with forlorn therapeutic hopes based on small trials. At the same time, the numerous side effects the author reports cannot be ignored.

There is another aspect of this paper which merits comment. It is not surprising that the author has encountered reactive phases of such difficulty as to prompt this trial while using a maintenance dose of DDS at the level of 100 mg. daily. Nowadays most leprologists would regard this dose as far too high, and would advocate a maintenance dose of not more than half this amount, with a very slow build up to that level. By such means the course of treatment is likely to be much more tranquil, and the incidence of reactive states materially reduced without loss of anti-bacterial activity. Where patients show any intolerance to lower doses of DDS some useful alternative drugs are now available for basic therapy. These facts provide additional fundamental grounds for questioning the necessity for this trial.

T. F. DAVEY

The Editor has asked me to comment on Dr Sheskin's paper which appears in this issue, and I would like to criticise it on the following grounds:

Firstly, the drug itself. Dr Sheskin is advocating the use of a drug which is so dangerous that, during the short time it was marketed, it left a trail of suffering and grief which stirred the conscience of the world almost as much as did the dropping of atom bombs on Japan in 1945. It is clear that Dr Sheskin confined his trial of thalidomide to males and to non-pregnant females, but, if more trials are carried out, there is a danger that the drug may inadvertently be given to females in the early stage of pregnancy, or, more likely, that it will find its way into households where it will not be kept under lock and key. Quite apart from thalidomide's teratogenic effects, it should be noted that the following side effects were encountered during the trial: drowsiness, constipation, dryness of oral and nasal mucosa, erythema of face and chest, oedema, and skin eruptions.

Secondly, the actual trial. In the first place, Dr Sheskin should describe what he means by the term 'lepra reaction'. Many use it to describe both types of reaction occurring in lepromatous leprosy, the one in which the actual leprosy

lesions rapidly become swollen and erythematous, and the other type characterised by erythema nodosum. I use the terms Type 1 and Type 2 to differentiate them (Jopling 1959), and at the 8th International Leprosy Congress in 1963 the respective terms 'lepromatous exacerbation' and 'lepra reaction' were recommended. Their response to treatment is different, and the reader of Dr Sheskin's paper needs to be told which of these two types of reaction was treated, or whether both types were included. Further, although we are told that the drug was given to 13 'unselected cases' we are not told what system was adopted to exclude bias. I do not think, therefore, that any conclusion can be drawn from this trial. However, recent work on skin homograft survival suggests that thalidomide possesses immunosuppressive properties (Hellmann *et al.*, 1965), so it is probable that more trials of the drug in lepra reaction will soon be under way and Dr Sheskin's results will either be confirmed or refuted.

I would like to say a final word on the use of dapsone (DDS) in patients who are reacting, for it would seem to me to be extremely hazardous to give 100 mg. daily to such patients. I would consider it unwise to give as much as 100 mg. *in one month*, let alone in one day, and anyone who tries giving 5 mg. twice a week will be taking the first step in getting the reactions under control and will be pleasurably surprised at the steady improvement in smears and biopsies.

W. H. JOPLING

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I have carefully read the paper of Dr Sheskin regarding the effect of thalidomide on the lepra reaction. I must admit that I know very little about leprosy but I find it intriguing that thalidomide should be found to possess yet another type of biological activity in addition to its well known embryotoxic, neurotoxic and sedative effects. It would be interesting to know whether there is a common biochemical denominator in all these effects or whether they are independant of each other. At present, in spite of intensive research, we know very little about how thalidomide produces its effects.

Thalidomide under physiological conditions is known to be a very reactive (unstable) compound and in the body it undergoes spontaneous hydrolysis to give some twelve metabolites all of which are known. It would be of great interest to know whether it is the drug itself which is responsible for suppressing the lepra reaction or whether this effect is due to one or more of the metabolities.

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Lep. Rev. (1965 **36,** 4, 189/206)

The Diagnosis of Leprosy with Special Reference to Tissue Defense

(Being the Stephen Rothman Memorial Lecture, 1964, Delivered at the Annual Meeting of the American Academy of Dermatology on December 6, 1964 by
R. G. COCHRANE, M.D., F.R.C.P., D.T.M. and H.)

INTRODUCTION

I cannot adequately express my sense of gratitude and privilege to be invited to give this Stephen Rothman Memorial lecture (1964). I only had the privilege of meeting Dr Rothman on three occasions when in Chicago, and the last time I saw him, he greeted me in terms of lighthearted humour which was so well known to his friends with the remark, 'Here is the person who tells me the cases of sarcoid among my negro patients in Illinois are most probably leprosy'. To have even this slight acquaintance with this remarkable personality leaves an indelible impression on one's mind. I gladly pay homage to one who was outstanding in his profession, a leader of men, and to borrow a phrase from Professor Lorincz, an unchallenged master of investigative dermatology.

I do not feel competent to address this Academy, but I trust that what I say will help in the better understanding of one of the most complex of all diseases. I shall endeavour to show that when clinical leprosy is related to a more detailed study of the pathology of disease, leprosy then becomes a magnificent tool for the elucidation of the many still unsolved problems in dermatological practice and particularly problems which are associated with the autoimmune diseases and the collagen disorders. By so doing, I shall be relating clinical observations to fundamental studies. Ladies and gentlemen, I think in this way I shall be following, in a very small way, the great master of dermatology in putting my footsteps into the broad path left by this giant of men of whom all his friends acclaim in terms of great enthusiasm, that here is a prince among investigative dermatologists. Well deserved tributes were showered on Professor Rothman not only because of his erudition, but because of his enchanting humanity and lively personality, and his outstanding qualities made Professor Rothman a scientist of very great merit, and a man of great popularity among his colleagues.

Pathogenesis

Before passing on to the more detailed consideration of my subject, it might be well to refer briefly to certain aspects of the pathogenesis of the disease and its direct bearing on the subject of this address.

It is generally accepted that the *M. leprae* is the causative organism of the disease but owing to the fact that it is a very lowly pathogen, probably having to pass through neural tissue (Schwann cells), before it becomes pathogenic, certain questions have arisen in the mind of many investigators during the last fifty or more years as to just what part the *M. leprae* plays in the picture of the disease.

The reason why certain early workers expressed doubts as to the *M. leprae* being the cause of leprosy is explained, if while not denying the presence and initial cause of leprosy being the *M. leprae*, we assume that this organism itself is a relatively harmless parasite first invading neural tissues particularly Schwann cells, and then the dermal tissues, and finally parasitizing the whole of the reticuloendothelial system. Its very presence seem to trigger off certain disease processes which precipitate the more serious manifestations and complications of leprosy. For instance, there are serum changes; for example, the presence of cryoprotein and the absence of alpha globulin link leprosy with the autoimmune diseases and collagen disorders, e.g. disseminated lupus erythematosis and rheumatoid arthritis.

The conclusion, therefore, to which one is forced, is that while the *M. leprae* is the causative organism of the disease, it appears to set up side reactions which make this mycobacterial in-

vader merely an onlooker quite unable to intervene in the disturbances which have been set up; it is rather like the person who throws a match on to dry and arid ground and sets going a forest fire. The match is the original cause, but the forest fire is the effect.

In other words, the presence of the Mycobacterium leprae merely serves to trigger a whole series of chain reactions which renders it rather a passive onlooker in a series of malignant processes for which the organism has been initially responsible. The study of leprosy should be closely linked with the general dermatological approach to disease and particular attention should be paid to its relationship with disorders of collagen, auto-immune processes, particularly in relation to disseminated lupus erythematosis, disorders of pigment such as pigmented nevi, and diseases related to non-specific clinical manifestations should not be overlooked. In addition to this, I note that a genetic approach to dermatological conditions is receiving considerable attention at this annual meeting of the American Academy of Dermatology.

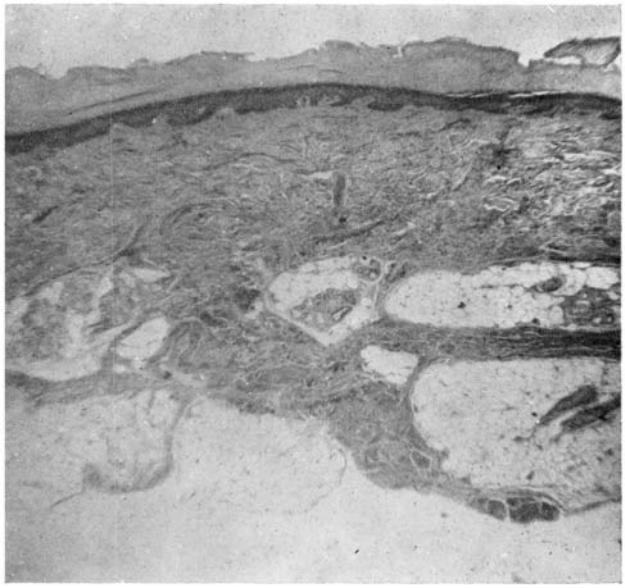
In this preamble to my main subject, I am making a plea for leprosy to be taken out of its splendid isolation, not only in the minds of men, but also from its separateness from the overall medical programme in our universities. This is the reason why I am particularly glad to be able to present to the leading dermatologists in the United States an approach to leprosy which, I hope, will convince them that it is a disease worth studying, not only for its own sake, but because of its impact on the whole field of medicine extending from anthropology, immunology, hypersensitivity, auto-immunization, the collagen disorders through to neural physiology, neuropathology, and the broad spectrum of reaction of the tissues to noxious influences. Therefore, if what I have said is in any way partly true, it is of the utmost importance that dermatologists should be acquainted with the earliest possible signs of leprosy for, as in all medicine, early diagnosis is the first pre-requisite to proper treatment and care of the leprosy patient. Even with our relatively effective remedies, we are still groping in the dark, and it is only in the light of pursuance of fundamental studies of leprosy that we shall begin to find our way to its ultimate eradication.

Before, however, detailing the early signs of the disease, I think it is fair to say that the great majority of persons, including medical men who first have to deal with leprosy, are a little perturbed in mind owing to the traditional fear of the disease, and this fear is very difficult to eradicate from the minds of men although there is no justification for such fears. There are altogether too many contradictory statements in regard to the infectivity or noninfectivity of leprosy. Therefore, it may not be out of place to refer to the fact that leprosy is a disease which is very rarely acquired. In fact, although some people say it is highly infective, other people say that it is not at all infective, and some people say that it is acquired by long and prolonged contact and that children are more susceptible than adults, others deny this; therefore, it may be of importance to call attention to these apparently contradictory statements, for in each of these statements, opposite though they may be, there is a very large element of truth. The truth is based on the fact that leprosy is a disease which is closely related to genetic susceptibility.

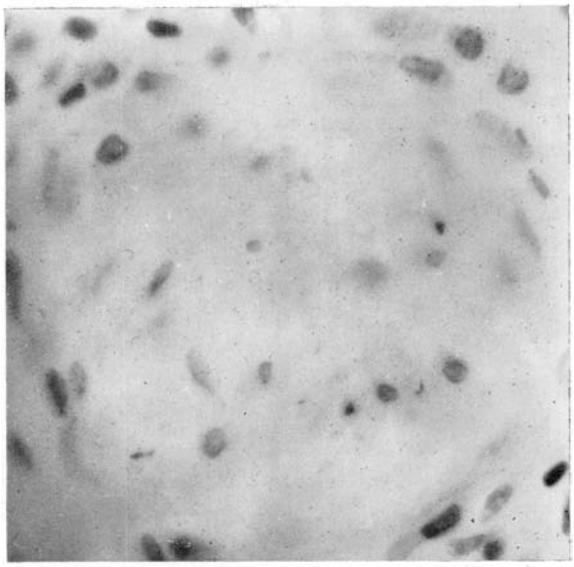
Early diagnosis of leprosy

As in leprosy, so in all diseases, the most important step is to diagnose the condition early. When I was a student we diagnosed early tuberculosis by means of the stethoscope. Nowadays, while the stethoscope is still a most useful instrument for the physician, no physician would attempt to diagnose early tuberculosis by this means. Today leprosy is in the same position that tuberculosis was 30 years ago, and the diagnosis of leprosy is always, or almost always, made too late and by the time the diagnosis is made, the patient has had the disease a very long time. For instance, the average time between the appearance of the first sign or symptom of leprosy in a patient and his treatment and diagnosis at Carville is seven years, and it may be as long as 20 years. This in itself underlines the importance that all physicians, particularly dermatologists, should be alerted to the very earliest evidence of the disease. If leprosy is diagnosed at the very earliest stage, then I am convinced it becomes a mere incident in a person's life, but if the diagnosis is delayed, then there is a danger of the disease becoming serious, crippling and deforming, because of the secondary effects produced by the *M. leprae* parasitizing the whole of the reticuleondothelial

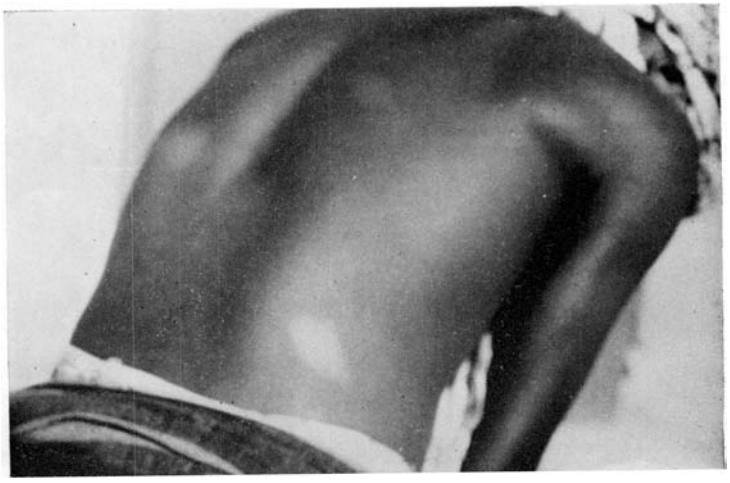
1 'Little abnormal to be seen underneath the epidermis or in the corium. There is some evidence of hyperkeratosis histopathologically but there was little evidence of this clinically'. (X200)



2 A Fite stain of the same section showing a nerve cut transversely deep in the corium, acid-fast bacilli were seen only in nerves, otherwise there were no acid-fast bacilli either in the superficial or the deep parts of the corium. (X900)

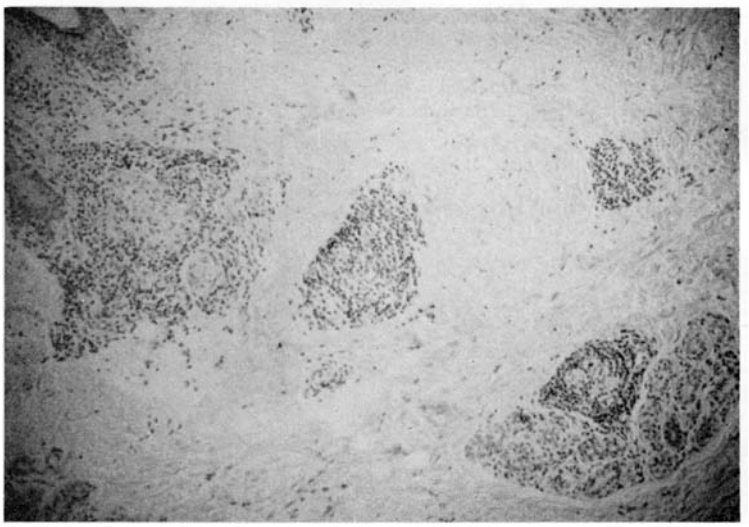


3 Lesions of indeterminate leprosy. Note the hypopigmented lesion in the right loin and another one at about the level of the fourth dorsal vertebra on the same side. The characteristic hypo-pigmentation and clearly defined edge is sufficient for those with experience to diagnose leprosy, but loss of tactile sensation (cotton wool) would confirm the diagnosis. On biopsy, careful search of serial sections might reveal an occasional bacillus, or group of bacilli, in a nerve in the corium.

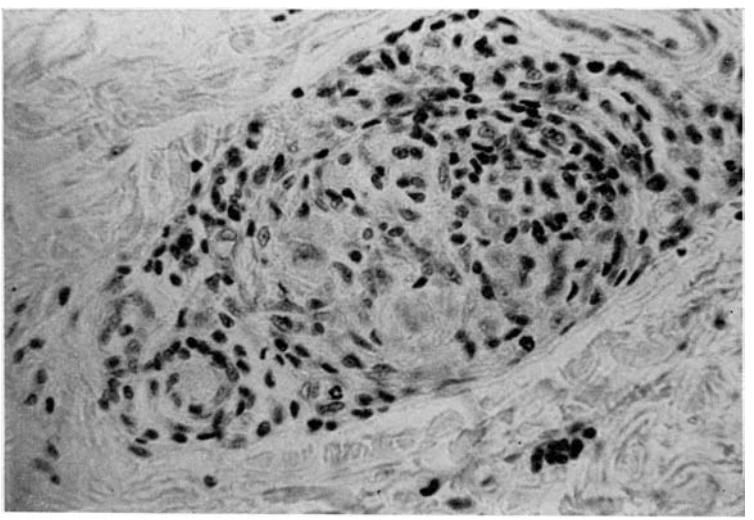


4 Maculo-anaesthetic leprosy. (Pre-tuberculoid macular leprosy). Note the clearly delineated lesion on the left cheek and forehead – this is an area which is not infrequently the primary site of infection in Africa, where mothers carry their children on their backs. There is also a maculo-anaesthetic lesion on the chin towards the left; there was no lesion on the right side of the face or elsewhere on the body, illustrating the asymmetrical tendency in maculo-anaesthetic leprosy.

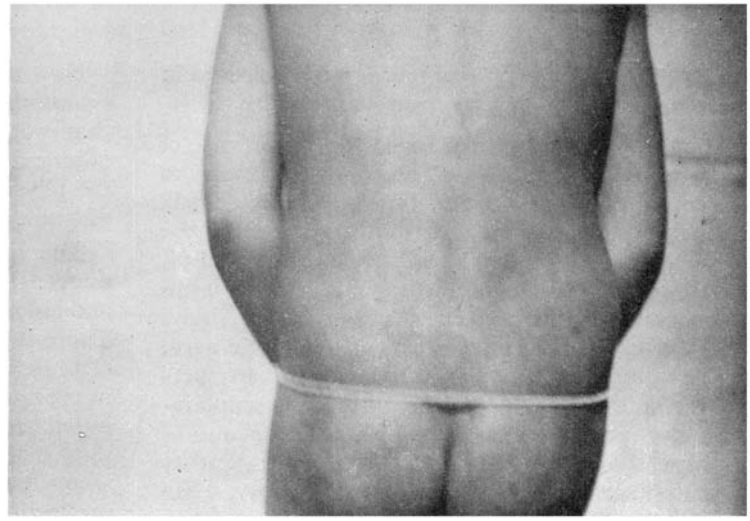
5 A histopatholgical picture of a classical maculo-anaesthetic lesion (pre-tuberculoid). Note the well marked lymphocytic infiltration around the skin appendages, also the area commencing epithelial cell formation at the base of the hair follicle with its well marked peripheral lymphocytic response. (X200)



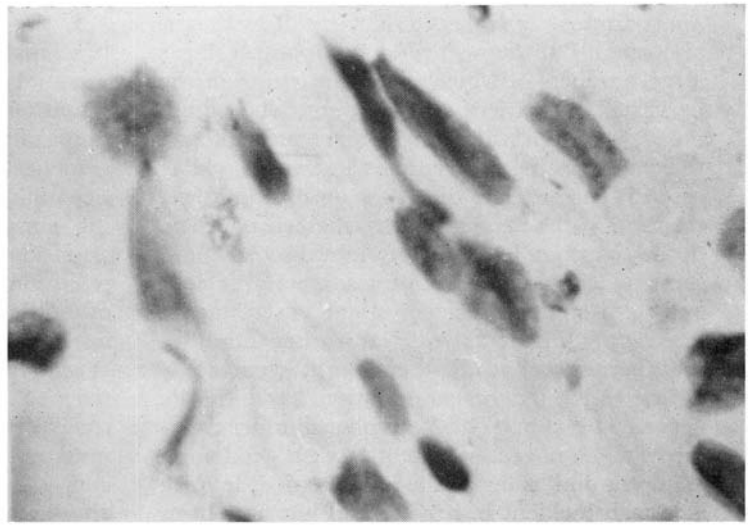
6 Photomicrograph of a nerve in the deeper part of the dermis of the same section as Illustration No. 5. Note the gross involvement of the nerve with epithelioid cells and the concentration of lymphocytes around the periphery of the nerve. The nerve is completely invaded by epithelioid cells and lymphocytes in a characteristic manner, hence the name pre-tuberculoid. This is a tuberculoid focus within a nerve. (X500)



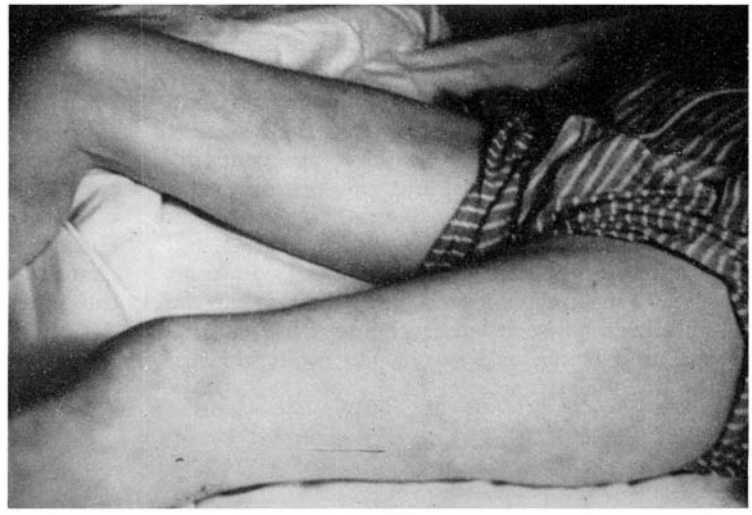
7 Pre-lepromatous macular leprosy. Note the numerous scattered macules all over the back, buttocks, and the arms, characteristic of this sub-type of lepromatous leprosy, showing very vague indefinite edges, symmetrical distribution and involving the whole of the surface of the trunk, buttocks and extremities.



8 Photomicrograph of a nerve deep in the dermis in a pre-lepromatous lesion. Note the enlarged Schwann cells and the bacilli within the nerve. It is not possible, apart from electron microscopy to say just where the bacilli lie. Some appear to be in the nerve (the axis cylinders), others are so close to the Schwann cells that it is almost certain they are within the cytoplasm of these cells. (X900)



9 Macular lepromatous leprosy. This is a further development from the pre-lepromatous phase in which the macules are much more definite and recognizable but still bear the same essential clinical features – multiplicity, symmetry and vagueness of the edge of the macule.



system of the body, and setting up conditions in the nerves which lead to gross crippling.

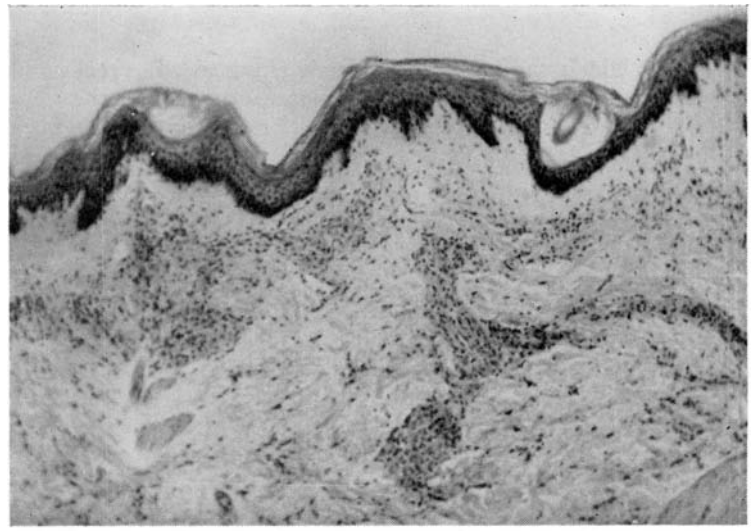
I have already emphasized the importance of neural tissue in leprosy, and I do not mean to enlarge on this subject, but it has been fairly conclusively shown that the target cell of the Mycobacterium leprae is the Schwann cell and, therefore, the first indication of leprosy is an affection of the peripheral nerves and it shows itself in the form of a numb or anesthetic area. It cannot be too often underlined that any person coming into a doctor's office and complaining of an anesthetic area, or a patch of numbness, should be investigated thoroughly lest he misses very early evidence of leprosy. The following illustrations will show the importance of making the diagnosis at this stage. The first is a photomicrograph of the skin which shows, apart from a little keratosis, very little that is abnormal. But the next photomicrograph shows large numbers of Mycobacterium leprae in the nerves of this patient. This patient, when diagnosed, was a girl of about 10 or 11 years of age, the contact being the mother who was a nodular case of leprosy. The daughter on examination, revealed at the base of the first metacarpal bone of the right hand an area of slight discoloration, showing less pigment than the surrounding area and with evidence of very slight loss of tactile sensation. The Resident was rather doubtful that there was anything there at all, so we took a biopsy and found, on examination, bacilli in the nerves. This young child was placed under treatment. She is now a woman of 22 with two bonny children, and as far as she is concerned, leprosy is just an incident in her life and has now been completely forgotten. In another instance, a missionary working in Africa wrote to me and said that he had an anesthetic area. I asked for a biopsy, and after about six hours searching serial sections, I came across twelve bacilli in a nerve. That is the time to diagnose leprosy, and if one misses a diagnosis at that stage, the next visible symptoms may be what are generally considered early signs, but are certainly not, that is the appearance of erythema nodosum lesions, with beginning of loss of eyebrows and stuffiness of the nose. These signs and symptoms always mean late leprosy and may mean the difference between leprosy being a lifelong disease and being, as I say, a passing incident in the life of a patient.

Now to turn to the more overt signs and symptoms of leprosy. While leprosy is more often than not missed in these early stages, there are other evidences of the disease which should alert the physician to the possibility of leprosy being diagnosed.

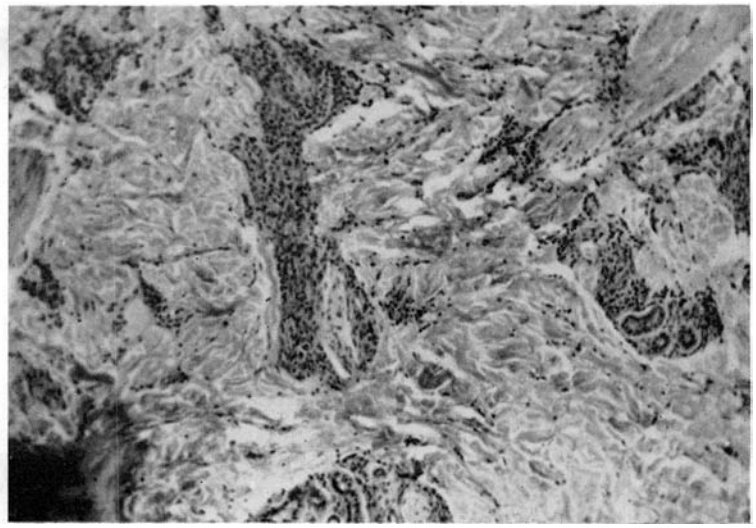
The signs and symptoms of leprosy can be divided into macular lesions, infiltrated lesions, and lesions associated with the peripheral nerves. There is one thing in common in regard to all of these visible evidences of the disease; that is in every case the clinical picture can be divided into those who show an exquisite tissue resistance, those who show no tissue resistance, and those who show a partial tissue resistance and on the proper interpretation of the tissue response depends the successful treatment and management of leprosy.

If the earliest sign of leprosy, almost in the preclinical phase, is to be diagnosed, it is essential that physicians should test for tactile sensation very carefully. Too often is the diagnosis of leprosy rejected because there is no evidence of loss of sensation using a pin. It must be emphasized, as all undoubtedly realize, testing sensation by a pin is not eleciting tactile sensation. It is eliciting light pressure and pain sensation, therefore, the only way to elicit loss of tactile sensation is to use a very light touch; for instance, a camel hair brush or a feather, or simply a small wisp of cotton – in Britain we refer to this as cotton wool. It also must be remembered, particularly in children, the patient must know exactly what the physician is doing and there must be very great patience in approaching a patient in the attempt to elicit the loss of tactile sensation. Even the youngest child will respond quite adequately, and sometimes the more sophisticated and intelligent the person is, the more difficult is it to get an adequate response. Where children are concerned it is very essential, as you all will realize, that the child must not be frightened and the best way to approach a child in respect to testing tactile sensibility is to play what I call 'a game of tickles'. Once one has got the confidence of a child, one very seldom finds any difficulty in eliciting loss of tactile sensation. This applies to the American, the British, the French, the African, the Chinese and the Indian child. They all respond perfectly well once a friendship is established between the little patient and the

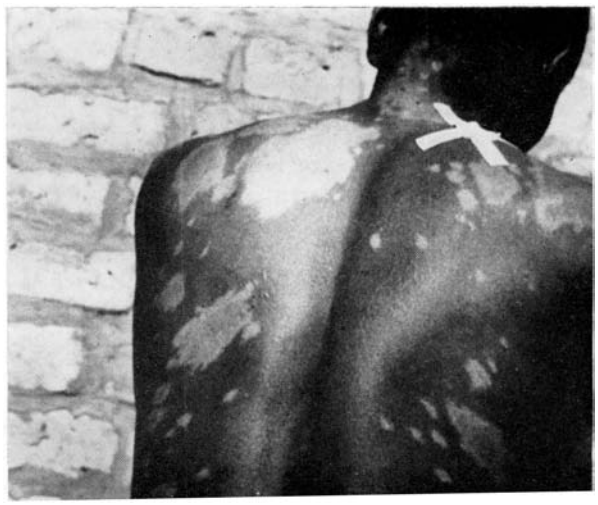
10 Characteristic histopathology of the early lepromatous macule. Note the scattered histiocytic and lymphocytic infiltration underneath the epidermis, leaving a relatively clear subepidermal zone. (X200)



11 Photomicrograph of the same lesion deeper in the dermis. Note the histiocytic and lymphocytic infiltration around the skin appendages with the nerves quite clearly standing out. The cells within these nerves are Schwann cells. (X200)



12 Dimorphous macular leprosy (sometimes called inderterminate leprosy). Note the multiplicity of the macular lesions, also that in the region of the scapulae the lesions have the appearance of maculo-anaesthetic leprosy in that they are large, with clear-cut edges. On the other hand, between the larger lesions and scattered all over the back are numerous small lesions with indefinite edges. The larger lesions represent the tuberculoid aspect of the dimorphous spectrum, whereas the small multiple macules illustrate the lepromatous aspect.



physician. It cannot be too strongly emphasized that taking a nasal smear does not necessarily establish a diagnosis of leprosy.

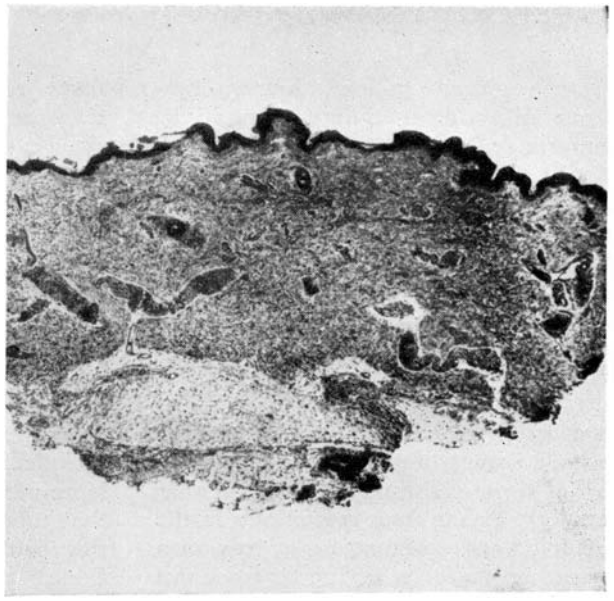
The finding of Mycobacterium leprae in the nasal mucosa is never, and I repeat, never one of the first evidences of the disease. Because of the numerous acid-fast and partially acid-fast contaminants in the nasal mucous membrane, to diagnose leprosy from such a smear is not only highly dangerous but extremely disturbing to the patient.

The diagnosis of leprosy must never be lightly made

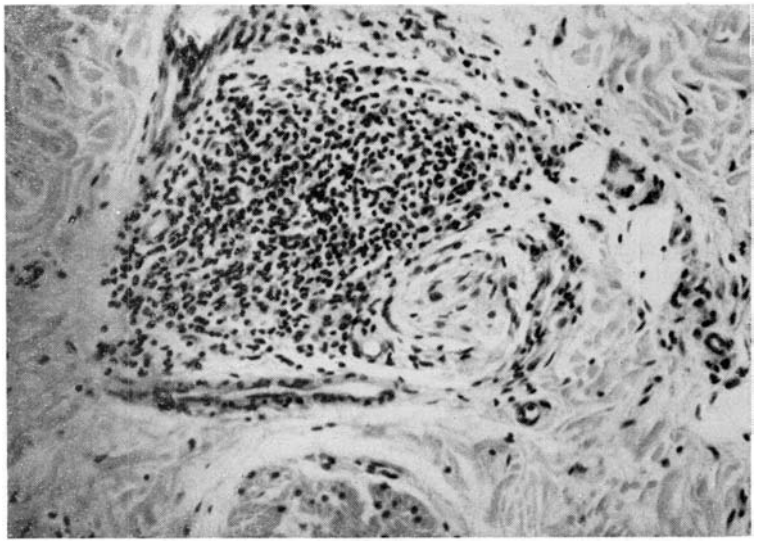
To turn to the clinical and histopathological evidence of leprosy in the macular phase, I would emphasize first that the very early macule is sometimes extremely difficult to diagnose. No examination should be complete without a biopsy. The following illustration shows a very early macular lesion of leprosy. A diagnosis could not be made except on clinical and histopathological evidence, and unless *M. leprae* were found, or there was early histologic changes suggestive of leprosy the lesion would have to be classified as 'suspicious' and the patient carefully watched. From this indeterminate macular phase, there are three lines of development. One, progress towards the development of an adequate tissue response; secondly, towards the development of an ineffective or absent tissue response; and, thirdly, towards the development of a partially effective tissue response. These three varieties of macular lesions are often described as maculo-anesthetic (pre-tuberculoid), pre-lepromatous and macular leprosy, and dimorphous (sometimes referred to incorrectly as indeterminate) macular leprosy. The next illustration shows the maculo-anesthetic lesion. Note the lesions on the face are well marked and clear cut and, while superficial tactile sensation is very difficult to elicit on the face, there was some evidence of loss of tactile sensation. But, on careful examination of such macules histopathologically, one is able to show that the essential tissues response is one of a commencing adequate tissue resistance, or the beginning of the evidence of a tuberculoid lesion and the next illustrations show the histopathology of one such lesion. Note the concentration of the lymphocytic and histiocytic response around the skin appendages and neuro-vascular bundles. Note the commencing attempting at forming epithelioid cells and, lastly, note the evidence of invasion of the nerves in the subcutaneous tissue showing the presence of epithelioid cells and one multinucleated epithelioid cell, establishing the diagnosis of leprosy.

The next illustration shows that form of leprosy in which there is absolutely no tissue response. There are multiple small macules scattered all over the body, on the front and back, and the trunk, almost impossible to recognize unless the patient, usually a child, is taken out into the sunlight or placed in a room with excellent artificial light. The bright light is directed obliquely onto the patient's back and then the small multiple erythematous macules stand out like little pieces of quartz shining in the sun. There is very little evidence of any loss of tactile sensation in the macules, but frequently if carefully tested, tactile sensation will be found to be diminished along the ulnar border of one or other hand or hands, or the outer border of the foot showing that both the ulnar and the common peroneal nerves are affected. Diagnosis is confirmed by the histopathological appearance of the lesions which in the earlier lesions show a non-specific inflammatory response, but bacilli are seen in the nerves and in the dermis; and in the later macular phases the histology is that of a moderate histiocytic and lymphocytic infiltration underneath the epidermis leaving a clear sub-epidermal zone. In the dermis proper, there is also a lymphocytic and histiocytic response, but note the nerves are very clear and are easily recognizable and within the dermis there are masses of acid-fast bacilli. These early lesions represent that form of macular leprosy in which there is no tissue response. I should add here that the lepromin test is not diagnostic, it only indicates the actual or potential presence or absence of tissue resistance in an individual. When the early lepromatous macular lesions begin to develop, then the characteristic macular appearance of leprosy is seen. The following is an illustration of early macular leprosy. Note the widespread distribution of the lesions, the very vague edge and a general erythema. In the dark skin, these lesions are much more difficult to recognize than in the light skin. But in the light skin, they are more often misdiagnosed for macular lesions due to allergic factors, erythema multiforme, or some other erythematous dermatologic condition which a dermatologist may see in his

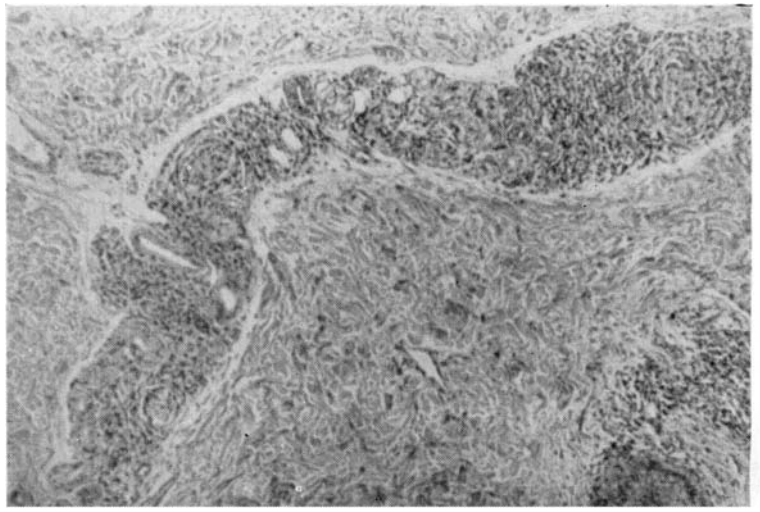
13 Photomicrograph of a dimorphous macular lesion. Note the lymphocytic and histiocytic infiltration tends to be concentrated around the skin appendages and vascular bundles. Also note that the infiltrate does not go up to the epidermis but tends to leave a relatively free sub-epidermal zone. (X100)



14 Photomicrograph of an area of the same section showing a well marked lymphocytic focus in the region of a neurovascular bundle. Note the intense accumulation of lymphocytes and a small nerve which shows no involvement stands out clearly, indicative of the lepromatous aspect of the dimorphous lesion. (X200)



15 This is a photomicrograph of the same section deep in the dermis. A long band of infiltration represents an area in the vicinity of a group of sweat glands. On the right there is an elliptical shaped structure which shows gross involvement with lymphocytes and histiocytes. This is the remnant of a nerve. On the left in the area of a blood vessel is another small nerve, again elliptical in shape. This shows much less involvement, nevertheless it is also partially invaded. In other words the nerves in this area are very difficult to recognize, and almost completely involved with a cellular infiltrate, lymphocytic and histiocytic, but there is little or no evidence of epithelioid cell formation. The infiltrate then in this area shows destruction and distortion of nerves and, therefore, represents the tuberculoid element of the dimorphous zone. Therefore, histopathologically and clinically, there are tuberculoid as well as lepromatous responses in this nerve, and in addition the nerve showed



office. Therefore, if any patient, presents himself in your office complaining of multiple, erythematous macular lesions which do not itch and do not fit into standard dermatologic diagnosis, and which do not respond to standard treatment, then remember leprosy and never, and I repeat, never omit a biopsy. When a biopsy is performed, never forget the precaution of having a section stained for acid-fast bacilli. If you do this, you will frequently get surprises, but you will not miss early macular lepromatous leprosy.

With regard to macular lesions of leprosy, there is a third variety of macular lesions which shows partial tissue resistance: that is, neither the potentially exquisite tissue response as in the pre-tuberculoid variety of macular leprosy, or a lack of tissue response as in the lepromatous type. This form of leprosy is sometimes called indeterminate macular leprosy. Dimorphous meaning both forms or shapes of lesions in the one person – tuberculoid and lepromatous, and histopathologically evidences of a partial tissue resistance. The following is an illustration of a classical dimorphous macular case of leprosy. Note that the larger hypopigmented lesions have a clear cut edge, they are large, and there is evidence of loss of tactile sensation and they occur in the areas which are most likely to be pressure points, the scapulae, the buttocks, the outer aspects of the extremities and the face. In between these larger macules, are groups of small macular lesions scattered over the trunk with lack of clearness of the edge. The edges, in fact, are somewhat fuzzy and usually do not show loss of sensation. When these lesions are biopsied and examined, the following is the general histopathologic picture: there is a scattered infiltrate underneath the epidermis with some evidence of a clear sub-epidermal zone. In the dermis, the infiltrate tends to be concentrated around the skin appendages and neurovascular bundles. Some nerves are grossly involved, others are free from infiltration. When an acid-fast section is done, not infrequently Mycobacterium leprae are seen in the nerves and sometimes in the tissues in varying numbers. These, then, are the macular lesions of leprosy and now we pass on to the infiltrated lesions.

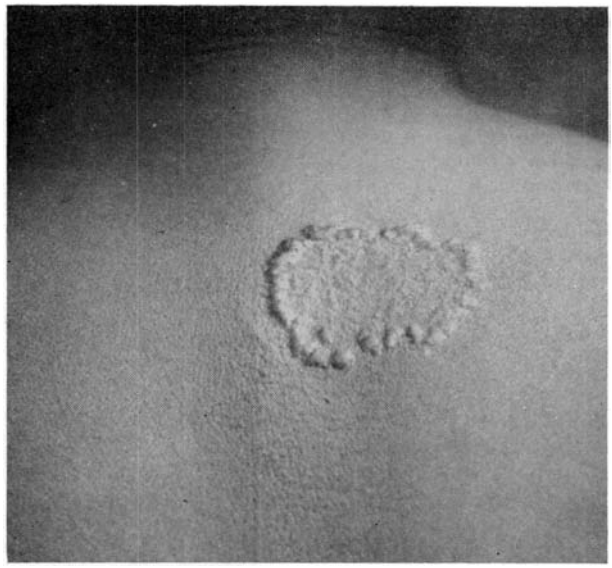
Infiltrated lesions

As in the macular phase of leprosy the lesions can be divided into those which show an exquisite tissue response, those which show no tissue response, and finally, those in whom there is some capability of putting up a tissue resistance of varying degrees. So then in all these lesions which are infiltrated, one sees the same tissue responses except that these are more exaggerated. There is generally a tendency in the Americas because of the paucity of the classical tuberculoid lesion, to place nearly all those lesions which are not lepromatous into the tuberculoid classification. If, however, tuberculoid means that form of the disease in which there is an adequate tissue response, then it is impossible to include all the raised lesions which are not lepromatous in this category. Many persons say that tuberculoid leprosy is a common form on this continent, but on the other hand, the Caucasian and Mongolian races belong to that group of persons, who, generally speaking, are unable to develop an adequate tissue resistance to the *M. leprae*. Also, I think it is fair to say that there are few absolutes in nature. Therefore, it seems logical that the largest group must be among those individuals who show a partial or dimorphous tissue response. It is my belief that the great majority of persons probably fall into the mid-zone, that is the dimorphous or as it is sometimes called, the border-line zone. The reason for this is because nature, as a rule, does not like absolutes.

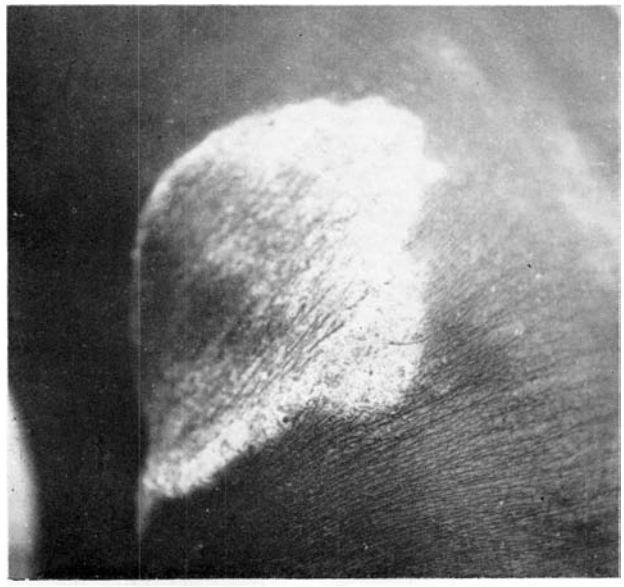
Tuberculoid leprosy

Tuberculoid leprosy is a manifestation of an exquisite tissue resistance and I have never personally seen a true tuberculoid case transform into lepromatous when the lesions are studied from the immunologic, histologic, and the clinical point of view. Tuberculoid leprosy then is seen in two sub-types. One, the established tuberculoid lesion and, two, disseminated tuberculoid lesion. Both forms of leprosy have a simliar clinical, immunologic, and histologic picture except that there are some slight variations which indicate that the histopathology and the clinical features are not quite the same. The established tuberculoid lesion is usually seen as a single lesion. If the infiltration is gross, then it is a major tuberculoid lesion. If the infiltration is slight, then it is a minor tuberculoid lesion. The chief characteristics of the lesions are that they occur as single, or not more than two lesions with very clear cut edges. There is absolutely no doubt about the edge of the lesion as is shown in

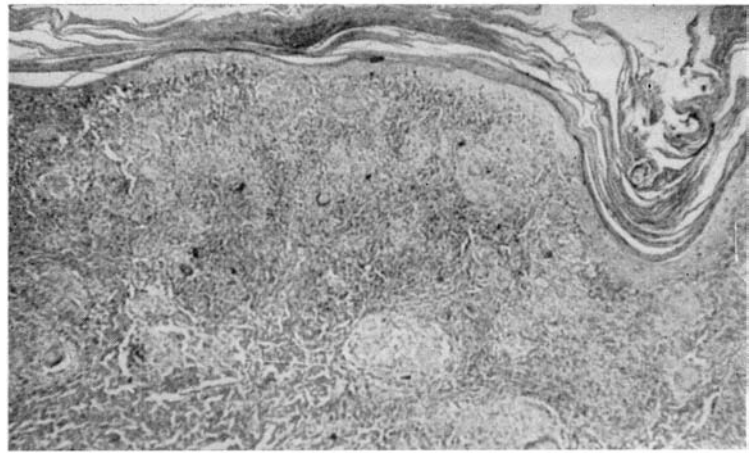
16 A lesion of established tuberculoid leprosy of minor grade. Note the peripheral papulated edge, clear-cut, with a central scarring or healing area indicating a centrifugal spread. No biopsy, unfortunately, was performed on this case, but it would have shown well marked and clear-cut epithelioid cell foci, not only immediately underneath the epidermis but in connection with the skin appendages and neurovascular bundles.



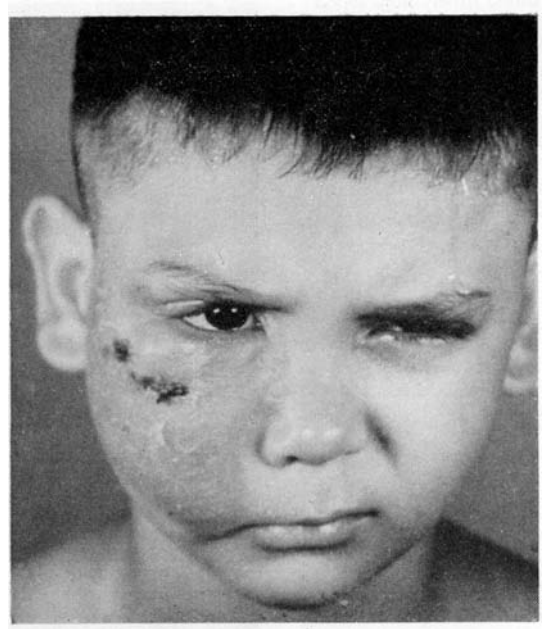
17 An excellent example of an established tuberculoid lesion. Note the large infiltrating plaque on the left back with clear-cut edges; note also that the lesion is beginning to show spontaneous regression.



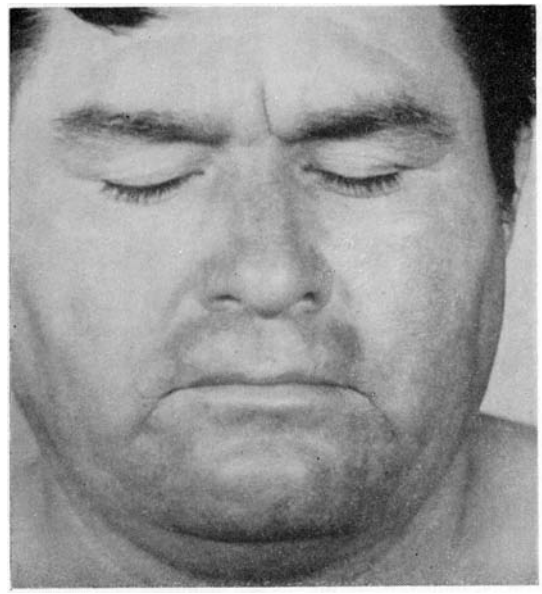
18 Photomicrograph of a biopsy from the edge of the same lesion. Note the massive granulomatous infiltration throughout the corium, the infiltrate extends up to the epidermis. There is no evidence whatever of any separation of the infiltrate from the epidermis. In other words the sub-epidermal area is absolutely obliterated. No nerves are recognizable. This gross granulomatous reaction results in the death of the bacilli and healing by scar tissue. In pre-sulphone days these lesions were not treated for when sulphones are used they have to be used extremely carefully and must not be given in the acute reactive phase or else further damage may result. (X200)



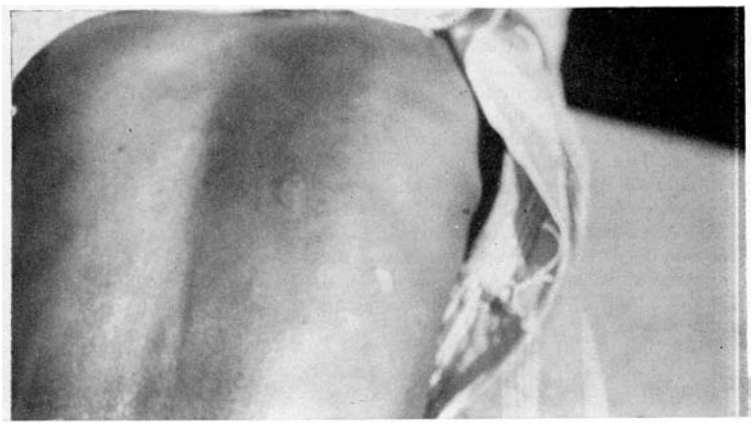
19 An established major tuberculoid lesion on the face showing an acute reaction which is beginning to subside. Note the ulcerated area and the gradual receding of inflammatory response at the edge of the lesion, also note the compensatory sweating on the left side of the face and the facial paralysis on the right. Had this boy been given a heavy dose of corticosteroids (the equivalent of 300 to 400 mg cortisone a week) the whole of the inflammatory response would have been damped down and the patient would have been saved facial palsy.



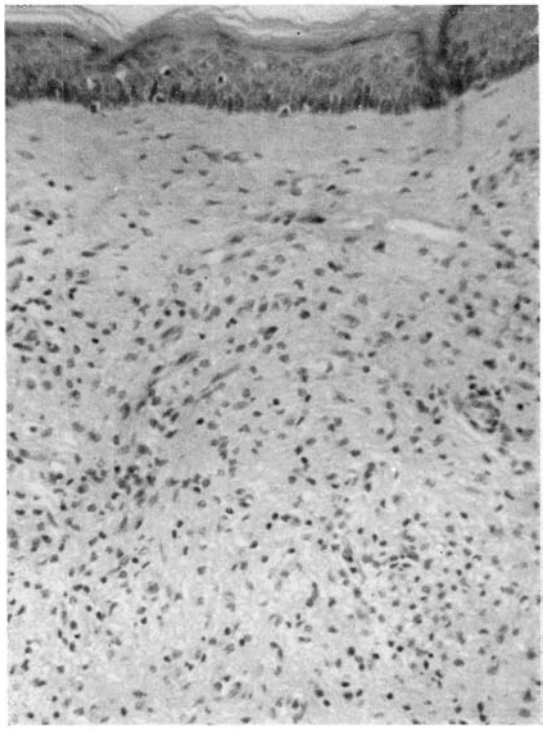
20 Diffuse lepromatous leprosy in a member of the Caucasian race. Note the puffiness of the face, the well marked eyebrows and a relatively smooth infiltration with no nodulation or grossly visible infiltrated areas. This form of leprosy is very deceptive for apart from a little puffiness of the face and some vague erythema the patient would not be recognized as having leprosy, although the skin and his nasal secretions would be full of acid-fast bacilli.



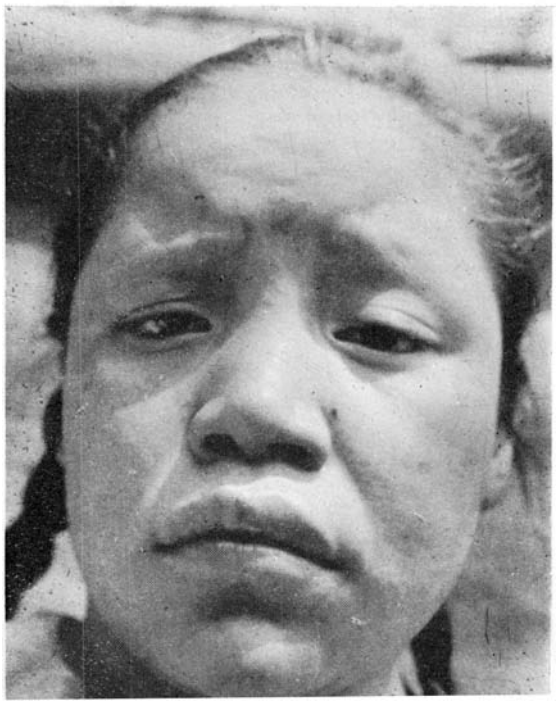
21 A diffuse lepromatous case in an Indian. Note the two white spots on the right back, these are scars of old injuries. Note also in the background of the diffuse lepromatous infiltration are residual macular lesions which, one would assume, were the original dimorphous lesions and all these have now largely coalesced to form a diffuse infiltration throughout the back, in fact throughout the body. Wherever a smear were taken it would be full of acid-fast bacilli. These diffuse lepromatous lesions constitute a considerable hazard, the patient looks well and healthy and only when the physician takes the patient out into the bright sunlight can a greasy, diffuse, lepromatous infiltration of the skin be recognized.



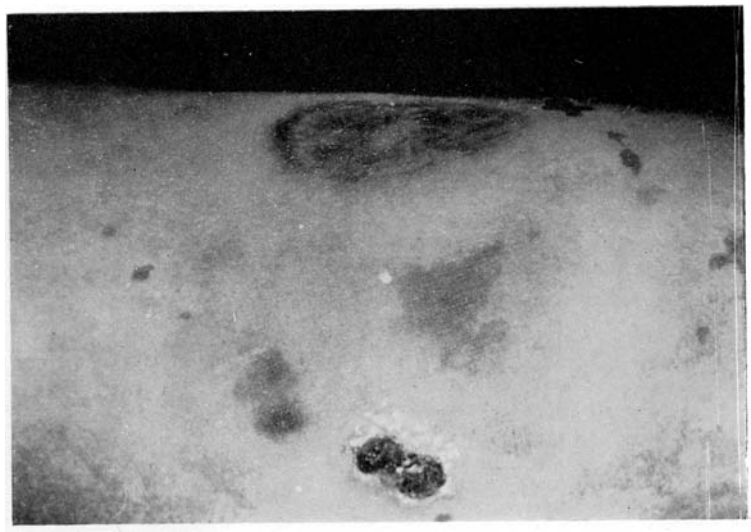
22 A photomicrograph of a diffuse lepromatous leprosy. Note that the whole dermis is occupied by a histiocytic infiltration with here and there scattered lymphocytes. The lymphocytic response is in no way focalised. Note also that the macrophage cells have a bubble appearance, this is characteristic of the early formation Virchow's foam cells. Here and there in the infiltrate are a few plasma cells. In such cases the ratio of serum albumin and serum globulin is reversed. (X200)



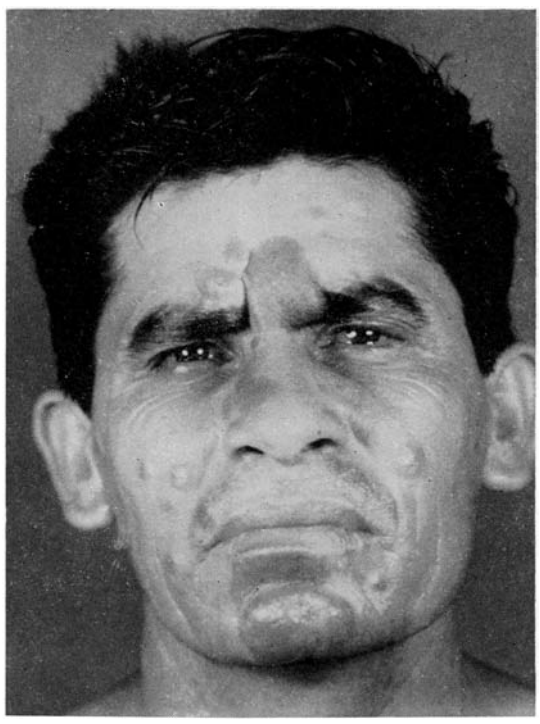
23 Diffuse lepromatosis of Lucio. This is a clinical sub-type of lepromatous leprosy seen almost exclusively in Latin America, particularly in Mexico. It manifests itself as a diffuse infiltration of the skin with no visible nodules or thickened areas. The patient is frowning and therefore the region of her eyebrows looks infiltrated. Actually the whole face has a smooth, greasy appearance with loss of eyebrows, loss of, or scanty, body hair. (Axillary and pubic).



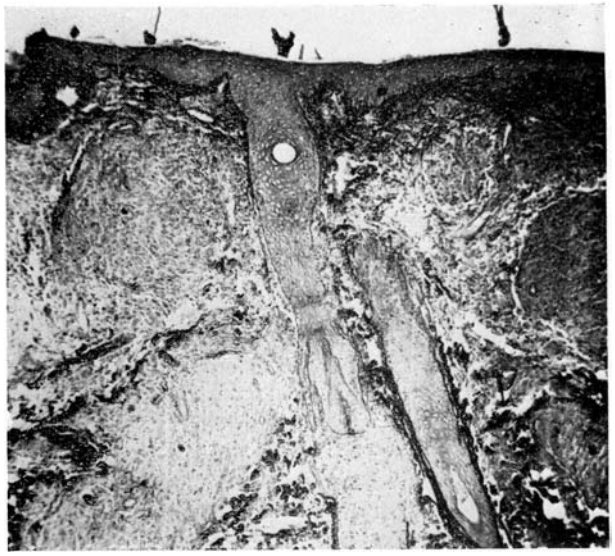
24 It is in this sub-type of lepromatous leprosy that the Lucio phenomenon is seen. The lesions start with an erythematous macule which soon becomes purpuric in appearance, then an ulcer forms and breaks down to the scab and shows the beginning of healing. In the days before sulphone therapy such cases usually died of amyloid disease.



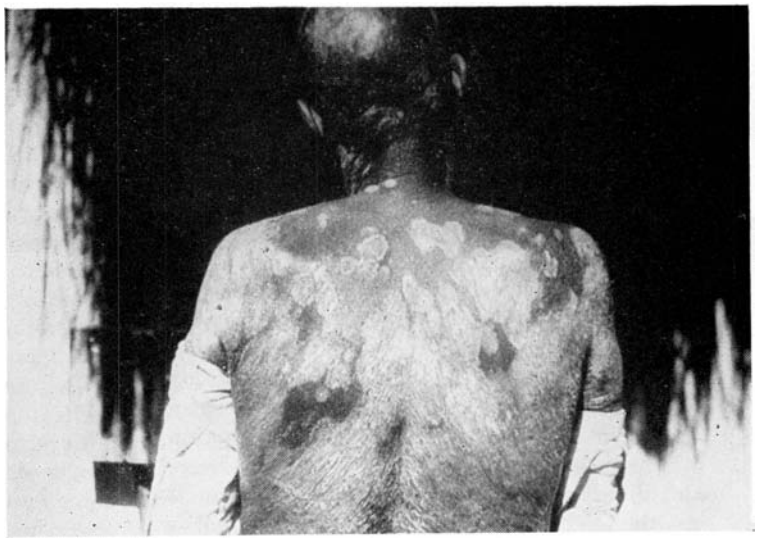
25 Infiltrated dimorphous leprosy on the tuberculoid side of the dimorphous spectrum. Note the relatively clear-cut lesions on the forehead and the characteristic dome shaped lesions on the chin and cheeks, and the widespread and symmetrical distribution of the lesions.



26 Histopathology of a dimorphous tuberculoid lesion. Note the clear sub-epidermal zone and the well marked epithelioid cell foci in the corium. The answer is a clear sub-epidermal zone and the lesion then is in the dimorphous zone no matter how 'tuberculoid' the lesion may appear clinically. (X200)



27 Disseminated tuberculoid leprosy. This is a form of tuberculoid leprosy which, clinically, has the appearance of tuberculoid leprosy but the lesions are multiple and disseminated all over the body, in other words, this sub-type of tuberculoid leprosy is spread by the blood stream.



28 The histopathology of disseminated tuberculoid leprosy. Note the partially obliterated sub-epidermal zone, the well marked foci of epithelioid cells with only a moderate lymphocytic response. In other words the focal distribution is not as clearly delineated by a peripheral lymphocytic response as seen in the established tuberculoid sub-type (Compare illustration 18, X200).

the following illustration. Anesthesia is always present and frequently there is enlargement of the subcutaneous nerve going to the lesion. When such a lesion passes into an acute reaction it has not infrequently been diagnosed as a cellulitis, or even an erysipelas. On careful examination, however, the features of tuberculoid leprosy will be indicated and almost certainly, the superficial cutaneous nerve to the affected area will be found to be enlarged. The following is an example of the type of tuberculoid lesion which could be mistaken for an acute cellulitis. The histopathological picture in such lesions is very definite. There is a gross infiltration occupying the whole of the corium. The sub-epidermal zone is completely blocked, as in this illustration, and this histopathology is also illustrated under the microscope. This form of leprosy, I feel, is probably related to that type of lupus, called lupus verrucosus, in which the infection comes ftom a direct innoculation either through the handling of infected meat or in the rare instance, of direct innoculation of those who are in attendance on patients suffering from 'open' tuberculosis (Ingram and Brain 1957). On the other hand, there is a form of tuberculoid leprosy which is disseminated by the blood stream. Instead of a lesion appearing at the place of innoculation, there are multiple lesions throughout the body. In such instances it is quite easy to surmise that if the tissue response is not quite so gross as in the established tuberculoid leprosy, then the occasional bacillus and, especially if the tuberculoid lesions go into reaction, may pass into a lymph node or a blood vessel and the disease becomes disseminated throughout the body. The features of disseminated or low resistant tuberculoid leprosy are very similar to that of the established form, except that the lesions are multiple, they are grossly infiltrated, and the edge is very clear. The following illustrates what I mean by disseminated or low resistant tuberculoid. The histopathologic picture is also illustrated under the microscope and in the photomicrographs I have set out. The main feature of the histopathology of this lesion is that, while there is a gross infiltrate occupying the shole of the dermis going up to the epidermis, but here and there, there is a looseness of the infiltration separating the granulomatous tissue in parts from the epidermis. In addition to this, there is a tendency for the lymphocytic element to be less manifest and the epithelioid cell reaction is in greater evidence.

Lepromatous leprosy

This is that form of leprosy which is placed at the other polar end of the spectrum, and it is seen in those infiltrated lesions which show no tissue response whatever. The tissues are anergic to the presence of the Mycobacterium leprae. There are two sub-types of infiltrated lepromatous leprosy; namely, diffuse lepromatous leprosy and grossly infiltrated, or nodular leprosy. I do not propose to describe the latter variety of leprosy because it is too well known to need any description, but the diffuse lepromatouse case of leprosy is of extreme importance to physicians and particularly to dermatologists because these lesions are very diffiult to recognize, and it needs a trained eye to be certain that one does not miss this potentially dangerous subtype of leprosy because the tissue response is so ineffective that the actual lesions are not seen. Diffuse lepromatous leprosy then manifests itself by a diffuse infiltration of the whole skin. The infiltration is felt rather than seen. If one picks up the skin between one's fingers one appreciates the generalized infiltration of the dermal tissues. These diffuse lepromatous cases are difficult to diagnose if one is not alerted to the condition. The following are examples of diffuse lepromatous leprosy.

Diffuse lepromatous leprosy is diagnosed by feel rather than by sight, because it is a diffuse infiltration of all the skin. The patient himself frequently does not feel ill, although there may be some nausea and slight increase in temperature when he goes into a reactive phase; but normally he can play games, build houses, hew down trees, and indulge in normal activities. Nevertheless, if a biopsy is taken of one such patient, there is usually found a large number of acid-fast bacilli. It is important, therefore, for practitioners to remember that this condition is very easily overlooked and if there is any cause to suspect that the patient has been in an endemic area of leprosy, then the simple precaution should be taken of taking smears from the ear, from the forehead, and if possible from the buttocks which would reveal at once the presence or absence of diffuse lepromatous leprosy. The only outward visible sign is a slight greasy-looking appearance of the skin, some change in the

eyebrows and nothing indicating any specific dermatological condition of the skin. There is no evidence of anesthesia except perhaps some numbness in the outer aspects of the hand (ulnar distribution), outer aspects of the foot (common peroneal distribution). It might be well to emphasize at this point that taking a nasal smear may not necessarily give the diagnosis for in early diffuse lepromatous leprosy, the nasal lesions may not be positive to routine methods of examination and, therefore, nasal smears should not be relied upon as a mode of confirming one's diagnosis. Histopathologically, there is diffuse infiltration throughout the dermis leaving a clear sub-epidermal zone. The infiltrate consists mainly of histiocytes of the large macrophage variety many of which show characteristic foamy cell change. In addition to this, the nerves are very well seen and when the section is stained by the Fite technique, acid-fast bacilli are seen throughout the dermis and the nerves.

This form of diffuse lepromatous leprosy must not be confused with the diffuse lepromatosis of the Lucio type. This form of diffuse lepromatous leprosy appears to occur only in the Latin American continent, particularly Mexico. Here, again, the skin has a diffuse greasy appearance and the infiltration is felt rather than seen, but in addition to this, there is gross loss of eyebrows, eyelashes, and body hair and it is in this type of diffuse lepromatous leprosy that the characteristic Lucio phenomenon appears which is a reactive phase of lepromatous leprosy. In fact, erythema modosum, panniculitis nodosa, and Lucio leprosy are all of a similar pathologic nature. Lucio leprosy is the most severe of all these forms and is seen as an obliterative endarteritis giving rise to the characteristic Lucio ulcer which occurs usually on the extremities, and was extremely difficult to treat, but now that we have sulfone therapy these lesions have largely lost their terror.

I have now reviewed the main features of lepromatous leprosy and I do not think that it is necessary for me to detail the clinical signs and symptoms of advanced infiltrated nodular leprosy for by the time a patient has reached this stage of advancement the disease should be easy of diagnosis.

I will now pass on to that form of leprosy which is described as *infiltrated dimorphous or borderline leprosy*. These clinical manifestations show themselves in lesions which have somewhat the appearance of an effective tissue response, i.e. tuberculoid leprosy, and lesions which simulate the general picture of lepramatous leprosy. It is in this area of the spectrum that considerable confusion arises in many person's minds. In 1936, Dr Wade styled this form of leprosy as 'borderline' while Lowe referred to those cases which were not definite tuberculoid or lepramatous as 'N?P'. In those days we divided leprosy into neural and cutaneous types. Just as the histopathologic picture is varied, so is the clinical for this is a very broad spectral band. Some lesions are very similar to tuberculoid lesions, whereas others are nearer to the lepromatous classification. It is because this zone is merely a part of the total spectrum of leprosy that one has designated it the dimorphous zone. The best way to describe the varied picture of this sub-group is by showing illustrated Kodachromes depicting the various clinical lesions. One thing one must bear in mind is that clinically the lesion may show well-marked infiltration, they may be plaque-like, but the edge of the lesion is never clear-cut and one has to look at the lesion and try and determine the most prominent part of that lesion. If the most prominent part of the lesion is away from the edge, even though it is just inside the edge, then the lesion histologically nor clinically nor immunologically is a true tuberculoid lesion. The importance of recognizing this dimorphous picture is because these are the most unstable of all clinical forms of leprosy and they have to be treated with the utmost caution.

In conclusion, Mr President, I have to remind this distinguished audience that the diagnosis of leprosy is relatively simple if it is remembered that the first presenting sign of the disease is anesthesia or numbness; also the physician must always be alert to the fact that any lesion which is slightly bizarre and does not fit into a standard dermatological diagnosis, leprosy must be ruled out before a firm diagnosis is made. Furthermore, the importance of recognizing the various tissue responses to the challenge of *M. leprae* cannot be too greatly stressed, for to place a lesion in the wrong classification may give rise to serious damage and mis-management of the whole treatment of the individual. It is sometimes the best policy not to treat at all. Also, in relation to the diagnosis of leprosy with special

reference to tissue response, there are certain forms of leprosy which are extremely unstable and the standard treatment of DDS or Dapsone may have to be withheld for a considerable time. Finally, it must be borne in mind that treatment is not easy and requires patience, persistence and time in order to overcome those numerous side effects which the presence of the Mycobacterium leprae triggers. Unless this is understood the diagnosis and management of a case of leprosy may end in, if not a disaster, very serious consequences to the patient in the nature of deformity and produce a psychological state of utter despair.

Furthermore, if it is true that the Mycobacterium leprae triggers off certain side reactions which are related to the auto-immune processes and to the collagen diseases, then one must be very cautious before administering corticosteroids. If they are administered they must be given in very small dosages. It has been shown that corticosteroids because of their ability to inhibit or depress lysosome activity frequently are responsible for the patient passing into a stage where, humanly speaking, the prognosis is hopeless.

I, once again, would emphasize very strongly that the initial symptom or sign of leprosy is numbness or anesthesia. If leprosy is diagnosed at this stage, then it may mean the difference between leprosy being merely a passing incident in life or years of agonizing failure ending in despair, deformity, and death.

Thank you, Mr President, for doing me the honour of requesting me to deliver this Stephen Rothman Memorial lecture and I trust that I have broadened your concept of the total picture of leprosy in relation to medicine in general and dermatology in particular.

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Characteristics of a Mycobacterium Strain (Chabotier) Isolated from a Leprosy Patient

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In 1939, at the Hospital St Louis, Paris, a skin biopsy was taken for examinations from a non-ulcerated ear-lobe lesion of a patient suffering from advanced lepromatous leprosy. Part of the biopsy material was put into sterile distilled water in a sterile tube which was then sealed and kept at room temperature. This material was later examined by Sister Marie-Suzanne and the author, and the bacteriological findings are described in the following report. In 1954 it was found that the tissue sample in water had disintegrated and smears from it and the supernatant liquid showed acid-fast bacilli and numerous homogenous cyanophil 'coccal' bodies. Cultures were made on Lowenstein-Jensen medium and on glycerol agar. After eight weeks at 37áC., a culture of a rough light-yellow *Mycobacterium* strain had developed on Lowenstein-Jensen medium. Smears showed the organism to consist of long acid-fast bacilli intermixed with non-acid fast cyanophil 'coccal' bodies. On glycerol agar, a whitish confluent growth was produced which included some wrinkled chromogenic areas. Smears from this growth showed shorter and more granular acid-fast bacilli and again these were mixed with 'coccal' elements.

The biopsy tissue in water was re-examined periodically up until the end of 1955 during which time a decrease in the numbers of cyanophil cocci was noted but there was an increase of fuchsinophil refringent granules a gradual increase in numbers of pleomorphic acid-fast bacilli was noted. In February 1956, a pure culture of the *Mycobacterium* strain was obtained on solid medium, the cyanophil elements no longer being apparent. The strain grew very sparsely in a liquid medium at first, but cultures in Sauton medium were later grown from the tissue in the form of a wrinkled light-yellow surface pellicle. Once again cyanophil cocci were interspersed with the acid-fast bacilli in this growth.

Subcultures from the Mycobacterium strain (named 'Chabotier') grew progressively more readily in serial transfers and a brief summary of their properties is given below.

Properties of the Mycobacterium strain ('Chabotier') subcultures

Bacillary morphology – Acid-fast cocco-bacilli

Colony morphology on Lowenstein-Jensen medium – Smooth glistening yellow colonies develop; pigment develops in dark as well as light.

Growth rate:

(a) Lowenstein-Jensen medium – Colonies begin to appear in 5 days at 37°C. and rather later at 26°C.

(b) Nutrient agar – Growth develops more slowly than in (a).

For comparison with other mycobacteria see Table I – Biochemical reactions (see Table II):

(a) Niacin production – Negative.

(b) Catalase test – Positive.

(c) Peroxidase test – Negative.

(d) Arylsulphatase test – Negative.

(e) Amidase tests (carried out by Dr E. Nassau, Harefield Hospital, Middlesex, England).

Only urea was split amongst the following substances tested: acetamide, benzamide, nicotinamide, succinamide, propionamide, valermide, pyrazinamide, urea.

Animal inoculation studies:

(a) *Guinea pig* inoculated intracardially with 1 mgm., of the moist culture showed no pathological changes when examined 12 weeks later Mantoux test using 1000 T.U. Weybridge PPD was negative 5 weeks after inoculation. (Carried out by Dr E. Nassau, Harefield Hospital, Middlesex, England).

(b) *Mouse* foot pad and muscle inoculation. The tests have been carried out by E. Palmer, R. J. W. Rees, G. Weddell (National Institute for Medical Research, London and Department of Human Anatomy, Oxford) and the results will be included in a separate paper by them.

CONCLUSION

The Mycobacterium strain ('Chabotier') may be described as urease-positive Scotochromogen (Runyon Group II). It is distinct from *Myco. marianum.*

TABLE I

Growth on Lowestein – Jensen Medium	*TEMPERATURE* Room			31°C.			37°C.			45°C.		
	4d	*2w*	*4w*	*4d*	*2w*	4w	*4d*	*2w*	*4w*	*4d*	*2w*	*4w*
Myco. 'Chabotier'	—	+	++	—	++	++	—	±	+	—	—	—
Myco. marianum	—	±	+	—	+	++	—	++	++	—	—	—
Myco. balnei	—	±	+	—	+	+	—	—	—	—	—	—
Myco. ulcerans	—	—	—	—	+	++	—	±	+	—	—	—
Anonymous mycobacteria												
Runyon Group I	—	±	+	—	+	++	—	++	+++	—	—	—
Runyon Group II	—	—	±	—	+	++	—	+	++	—	—	—
Runyon Group III	—	—	—	—	—	±	—	±	+	—	—	—
Myco. fortuitum	+	++	+++	+	++	+++	+	++	+++	—	—	—
Myco. tuberculosis H37Rv	—	—	—	—	—	±	—	++	+++	—	—	—
Myco. smegmatis	+	++	+++	+	++	+++	++	+++	+++	+	++	+++
Myco. phlei	+	++	+++	+	++	+++	++	+++	+++	++	++	+++

4d = 4 *days; 2w* = 2 *weeks; 4w* = 4 *weeks.*

TABLE II

	Niacin production	*Catalase activity*	*Peroxidase test*	*Aryl-sulphatase test*
Myco. 'Chabotier'	o	+	o	o
Myco. marianum	o	++	o	o
Myco. balnei	o	+	o	+
Myco. ulcerans	o	+	+	o
Anonymous mycobacteria				
Runyon Group I	o	+	o	+
Runyon Group II	o	+	o	o
Runyon Group III	o	+	++	+
Myco. fortuitum	o	+++	o	++
Myco. tuberculoiss H37Rv	+	+	++	o
Myco. smegmatis	o	+	o	o
Myco. phlei	o	+	o	o

DISCUSSION

The isolation of Anonymous mycobacteria and Saprophytic mycobacteria strains from the lesions of patients suffering from leprosy has been recorded from time to time, particularly from ulcerated areas. The purpose of the present report is to stress the need for detailed studies on such strains since, at the moment, they are often not adequately investigated in the fields of leprosy and dermatology. In the study of patients with respiratory diseases much work has been done on the various mycobacteria but even here the role of Anonymous mycobacteria is still not fully elucidated. Furthermore, there is insufficient information on their incidence in different parts of the world, particularly in tropical areas.

The incidence of Anonymous mycobacteria varies with individual investigations. In Britain, of 3,000 strains of mycobacteria studied in the Public Health Laboratory Service (1962), almost all from sputa of 'new' patients, 1.4% were considered to be 'clinically significant' Anonymous organisms and a further 1.1% were 'non-significant'. In a Lagos study by Beer and Davis, (1965) 6% of cultures of mycobacteria isolated in the course of routine examination of sputa were anonymous in type, mostly Runyon Groups III and IV. Recordings such as these are probably a gross under-estimate of the true incidence of these strains. It is probably true to say that in skin diseases the division between what are clinically significant Anonymous mycobacteria and what are merely commensal organisms or saprophytes has received only very limited study.

Whereas the photochromogenic Runyon Group I strains (*Myco. kansasii*) are probably the most significant pulmonary pathogens, Group III (Battey type) organisms are also well-known as causes of tuberculosis-like disease. The scotochromogens (Group II) and Rapid Growers (Group IV) are considered to be usually commensals or saprophytes, but the former is well known as a cause of scrofula-like cervical lymphadenitis particularly in debilitated subjects. Not included amongst the Runyon Group strains are the skin pathogens *Myco. balnei* (Linell and Norden, 1954) which is scotochromogenic and *Myco. ulcerans* (MacCallum *et al*, 1948) which is not pigmented. *Mycobacterium marianum* (Marie-Suzanne *et al*, 1952) appears to be an Anonymous mycobacterium and this was isolated from a non-ulcerated lesion of a leprosy patient. The heterogeneity of many of these 'strains' is exemplified by the recent work of Navalkar *et al*, (1964) who showed that *Myco. marianum* strains may differ in their mycoside content.

In this study of the scotochromogen 'Chabotier' it is impossible to conclude whether the organism was a contaminant which gained entry at the time of biopsy or later during subculturing, or whether it was present in the ear-lobe lesion of the leprosy patient concerned. It is a fact that the amidase test results reported above suggest it is a 'human' strain, but it is also known that some scotochromogens split urea whereas others do not. The value of amidase tests in this respect is still a matter of controversy.

The 'coccal' elements and 'granules' seen at different stages of culture of the 'Chabotier' chromogen may possibly have been of similar nature to those described by Csillag (1963). These develop in rapidly-growing organisms which are not acid-fast during stages in the culture of *Myco. tuberculosis* and Anonymous mycobacteria. They resemble the endospores of Bacillaceae. Czillag reported that a *Myco. tuberculosis* $H_{37}Rv$ strain which had been maintained for many years on Lowenstein-Jensen medium yielded sporulating forms only after 27 weeks incubation. This aspect of the 'Chabotier' organism was not pursued in this study.

Browne (1964) has emphasised the practical bacteriological difficulties in the investigation of leprosy patients, and has stressed the high value of recently developed laboratory investigations in the Genus *Mycobacterium*.

SUMMARY

A Mycobacterium strain ('Chabotier') isolated from the biopsy specimen of a non-ulcerated ear-lobe lesion of a patient who suffered from lepromatous leprosy is described and compared with other Mycobacterium strains. It is concluded that the organism is a urease positive scotochromogen of Runyon Group II. It is distinct from *Myco. marianum*.

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Leprosy and A.B.O. Blood Groups

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Alexander (1921) was one of the first who attempted to find a relationship between ABO blood group and disease. He found that group B and AB were peculiarly susceptible to various forms of neoplasms. Buchnan and Higley (1921) reported in the same year that there was no relationship between the blood groups and a disease. Johannsen (1925) stated that A and AB individuals were more susceptible to external influences provoking carcinoma of uterus while those of O and B were resistant. Mitra (1933) did not find any relation between blood groups and diseases except in helminthesis and malignancy where one AB blood group was predominant.

Since then there have been various reports of widely different conclusions on many diseases in relation to blood groups (Goldfeder and Fershing, 1937; Tinney and Watkins, 1941; Roberts, 1953; Aird *et al.*, 1953; Macafee, 1960; Beasley, 1960; Stirling, 1960, etc).

With the increasing interest in the rôle of genetic factors in the development of diseases renewed efforts are being directed towards determining the relationship of blood groups to diseases. Recently Hsuen *et al.* (1963) from South India have reported that there is an association between the incidence of leprosy and the ABO blood groups and the incidence of leprosy is nearly twice as high in O group as compared to the B group.

As there has been diversity of the results about association between ABO blood groups and various diseases, it was thought that studies undertaken on similar lines, in different parts of India, would be worthwhile.

Such a study was conducted in Baroda, a city in Gujarat State, in the Western part of India.

MATERIAL AND METHOD

The Blood group frequencies of 594 patients suffering from leprosy was determined. All the patients taken in this study belonged to Baroda district. They were either attending the Medical College Hospital, Baroda or one of the leprosy clinics in the district.

In the control series 1000 first time blood donors at Medical College Hospital were taken for the blood group frequency examination. Only those donors who belonged to Baroda district were included in this study. None of these donors has shown any clinical evidence of leprosy.

Blood was obtained by the finger prick method in all these cases, and was examined within a period of 6 hours. The diagnosis of leprosy and its type was determined by a thorough physical examination and bacterial index. Where a difficulty in the diagnosis arose, histopathological examination was performed. International classification was used for classifying the cases under study.

RESULTS AND DISCUSSION

Table I shows the frequency distribution of different types of leprosy among the 594 patients.

TABLE I

Frequency distribution of different types leprosy among the 594 patients

Type of disease	*No. of cases*
Lepromatous	288
Non-lepromatous	306
(1) Tuberculoid	151
(2) Borderline	66
(3) Indeterminate	87
(4) Neural	2

Table II gives the frequency distribution of blood groups for the control series, study series (Lepromatous) and study series (Non-lepromatous).

TABLE II

Blood group distribution of 1000 first time blood donors, 288 Lepromatous leprosy and 306 Non-lepromatous leprosy patients

Blood group	*Control series*		*Lepromatous*		*Non-lepromatous*		*Combined series*	
	No. of cases	%	*No. of cases*	%	*No. of cases*	%	*No. of cases*	%
A	242	24.2	74	25.7	82	26.8	156	38.9
B	347	34.7	111	38.5	120	39.2	231	26.3
O	355	33.5	92	31.9	85	27.8	177	29.8
AB	76	7.6	11	3.8	19	6.2	30	5.0
Total	1000	100%	288	100%	306	100%	594	100%

The value of $X^2 = 9.84$, for d.f. $= 6$ gives probability $p = 0.11$ as shown in Table II. The distribution of the blood groups between the three series do not differ significantly. This suggests that there is no association between the blood groups and the incidence of leprosy.

If we combine the two series (of Table II), namely, that of lepromatous patients and non-lepromatous patients and compare it with the control series, then the value of $X^2 = 7.86$, $p = 0.0496$, d.f. $= 3$ is arrived at showing that the difference is just significant. The probability being just 0.05, there is only a weak evidence that the blood group distribution among the two series (control and combined) differs. In view of the further analysis which follows in Table III this evidence becomes much weaker and we cannot accept the hypothesis that the distribution of blood groups in the two series differs significantly.

TABLE III

	d.f.	X^2
Sum of two X^2 from Table 2 (Cols. 3 and 4)	6	$6.09 + 5.03 = 11.12$
X^2 from Table 2 (Cols. 2 and 5)	3	7.86
Heterogeneity X^2 (difference)	3	3.26

Heterogeneity X^2 is 3.26 for d.f. $= 3$ gives $p = 0.20$, showing that the two lepromatous and non-lepromatous series do not differ significantly, as already shown in the analysis of Table II. Hence the conclusion from the addition of two X^2, namely 11.12, $p = 0.096$ for d.f. $= 6$ is more reliable than the result from the pooled data which gives $X^2 = 7.86$ for d.f. $= 3$. As mentioned earlier, this supports the hypothesis that the blood group distribution of the control series and that in the leprosy patients series do not differ significantly.

This work is almost similar to Hsuen *et al.*, study in its design and methodology. On statistical analysis of our results we are unable to confirm Hsuen's conclusion that there was an association between leprosy and ABO blood groups. Our results indicate that there is no difference in the incidence of leprosy between the ABO blood groups.

CONCLUSION

The blood group distribution of leprosy patients does not differ significantly from that of the general population. The data given here does not support the hypothesis that there is any difference in the incidence of leprosy between the ABO blood groups.

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Reconstruction of the Nose in Leprosy Patients

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The pathology of the nasal deformity which occurs in leprosy patients has been well described by Antia (1963) and others. The end result is a loss of lining of the nose with a perforation and absorption of the septum and partial absorption and depression of the nasal bones. The soft tissues and the skin usually remain complete and if freed from the underlying skeleton can be pulled out into the normal shape of a nose. Once this has been done there are three further requirements:

(1) To provide a new lining for the nose.

(2) To provide a new support for the crest of the nose and the columella.

(3) To fill in the space at the upper end of the nose in front of the nasal bones.

(1) *Provision of a new lining*

This is achieved by following the principles of the posterior nasal epithelial inlay as devised by Gillies.

(2) *Provision of a new support for the crest of the nose and columella*

Various methods have been used:

(i) A cartilage strut graft. Late results have shown that this is often extruded or absorbed in leprosy patients.

(ii) A plastic material used as a graft. These also are frequently extruded or become infected.

(iii) A removable prosthesis which is perforated to provide an airway. The results of this are good, but facilities are needed for the making of a prosthesis and a permanent opening has to be provided in the naso-labial sulcus for inserting and removing the prosthesis.

(iv) A crest graft of compact and cancellous bone obtained from the iliac crest and a columellar strut inserted through a columellar incision. This has the disadvantage in that it is very difficult to avoid having a ridge of bone showing at the end of the operation particularly in the upper part of the nose.

(v) A spear-head shaped cantilever graft obtained from the olecranon as described by Antia, inserted through an incision at the root of the nose and fixed by wire to the nasal bone. The results of this are good because the space at the root of the nose is filled out by the graft, but it has to be done as a second stage operation after having done a posterior nasal epithelial inlay.

(3) *Filling in of the space at the root of the nose*

No satisfactory procedure has yet been described apart from the above mentioned cantilever olecranon graft devised by Antia.

The cockett operation

The operation about to be described was devised by Dr Norman Cockett, FFARCS, when he was working at Mysore and Dichpalli in 1959. The operation is a one stage operation using a posterior nasal epithelial inlay and bone grafts for the bridge of the nose and columella obtained from the iliac crest, the innovation being the filling in of the space at the upper end of the nose in front of the nasal bone with minute chips of cartilage obtained from the costal margin.

Operative details

The patient is given a thorough dental toilet.

Anaesthetic. The operations have all been done under a lytic cocktail. For an average adult Morphia gr. $\frac{1}{4}$ and Hyoscine has been given S.C.I. one hour before operation. A lytic cocktail of Pethidine Mgm. 100, Chlorpromazine (Largactil) Mgm. 50, and Promezathine (Phenergan) Mgm. 50 has been made diluted to 20 ml. with normal saline (the Promezathine (Phenergan) has been omitted frequently with small sized patients). An intravenous drip of normal saline has been set up and 15 minutes

after the morphia and hyoscine has been given, 5 ml. of the cocktail has been given into the drip tubing and the dose has been repeated at 15 minute intervals until the total amount is given. After the second dose the patient has been tilted in the 45 degree head-up position to obtain postural hypotension. After the third dose the cords have been sprayed with 2 ml. of 4 per cent Lignocaine and the trachea has been intubated with a cuffed tube which has been inflated. The pharynx has been packed with gauze. On occasions the tube has been connected to a closed circuit anaesthetic machine with a flow of nitrous oxide and oxygen, but many cases have been done without this. Occasionally the patient may require a small dose of thiopentone during the operation but this has been rare. Flaxedil 40 Mgm. has been given to help with suturing the muscle layer after taking the iliac crest graft. A sand bag is placed behind the right buttock to elevate the iliac crest.

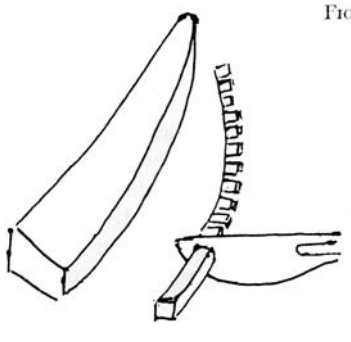
Taking of the grafts

(i) Bone graft

This is taken from the inner half of the iliac crest at its anterior end on the right side and includes part of the inner table resulting in an oblong graft about 2 in. long and $1\frac{1}{4}$ in. broad. The graft is taken with an osteotome making the two vertical cuts at the end of the graft first, a horizontal cut on the inner table next, and finally a cut along the length of the middle of the iliac crest between the vertical cuts to elevate the graft.

(ii) Cartilage graft

FIG. I.

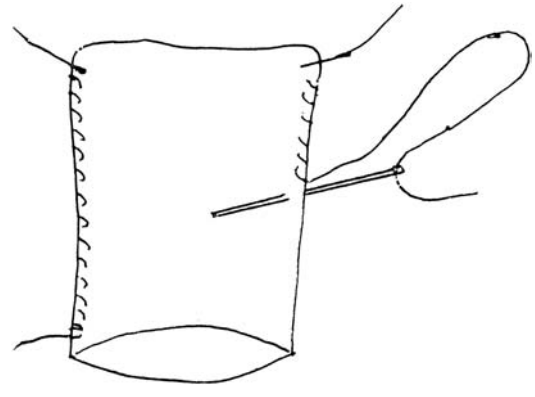


CUTTING OF CARTILAGE CUBES

A length of costal cartilage about 2 in. long is taken from the right costal margin.

The two incisions for taking the above grafts are closed.

(iii) Skin graft



SKIN GRAFT BAG FIG. II.

A split skin graft 3 in. $\times$ $1\frac{1}{4}$ in. approximately is taken from the right thigh.

The above grafts are placed in a solution of 2 per cent chloramphenicol in saline while the rest of the operation proceeds.

Freeing of the nose

An incision is made in the naso-labial sulcus sufficiently in front of the maxilla to leave enough mucosa posteriorly to hold sutures. The nose is freed from its skeletal attachments as far up as the glabella and pulled out into shape. The attachments of the bridge of the nose in particular are freed – small curved Mayo scissors are used for this purpose. The upper part of the perforated septum is divided as far back as possible where it joins the nasal bone leaving a small portion still attached anteriorly. The space thus formed is packed with ribbon-gauze and left for a while.

Preparation and insertion of the cartilage and skin grafts

The cartilage is cut into match-stick like strips which are cut across into tiny cubes – it helps if the perichondrium is not divided so that the cubes are still attached to one another rather like paper chains.

The skin graft is folded in half on itself to make a bag with the epithelial surface inside

and the two sides are sewn up with a continuous fine thread suture leaving the end open. The bag is packed with very small pledgets of cotton wool squeezed out in a 2 per cent chloramphenicol suspension in paraffin.

The gauze pack is then removed from within the nose and the nose is held forwards with a Langenbeck retractor inserted through the naso-labial sulcus. The space between the bridge of the nose and the nasal bones is then packed with the cartilage cubes and then the skin bag is put into the lower part of the post nasal space with its open end downwards. More pledgets of cotton wool squeezed out in chloramphenicol suspension are packed into the bag until the post nasal cavity is filled out and the nose assumes the desired shape. The free edges of the open end of the skin bag are then folded over one another and the incision in the naso-labial sulcus is closed with interrupted catgut.

Preparation and insertion of the bone graft

A columellar incision is made and with enucleation scissors a tunnel is made along the crest of the nose up to the glabella, and another small tunnel backwards along the columella as far as the maxilla. The length of the grafts required for the crest and the columella is gauged from the depth to which the scissors can be inserted.

COCKETT OPERATION

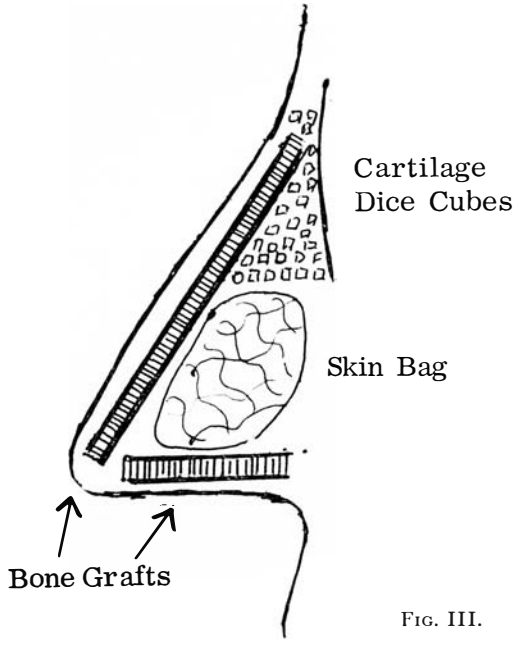


Fig. III.

INTRODUCTION OF BONE GRAFT

Fig. IV.

A graft of the correct length for the crest of the nose and about $\frac{1}{4}$ in. wide is cut from the iliac bone including the ridge of compact bone belonging to the crest of the ileum. This is trimmed and then introduced into the prepared tunnel. It can be slid into place between the blades of an opened-up pair of plain dissecting forceps placed in the tunnel, or a special introducer can be used. The graft is rotated so that the cortical bone faces anteriorly.

A smaller graft is now cut for the columella. A pair of non-toothed dissecting forceps is placed in the columellar tunnel and the graft is slid into place between the blades of these forceps. The upper end is lodged under the

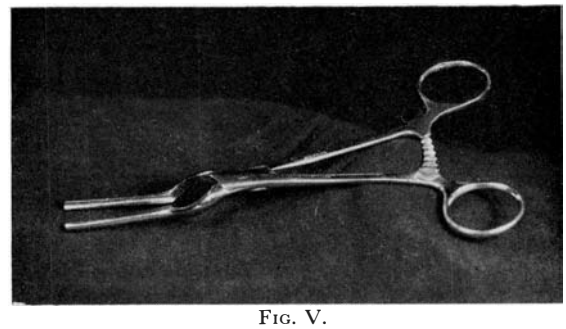


Fig. V.

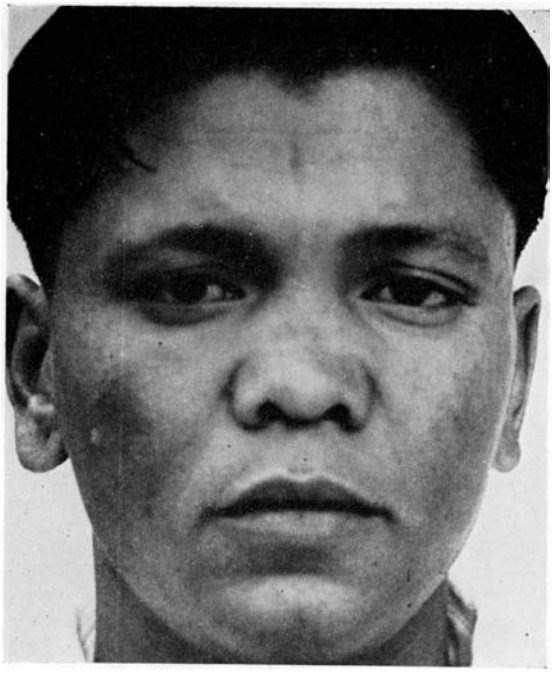


FIG. 6. Before operation.

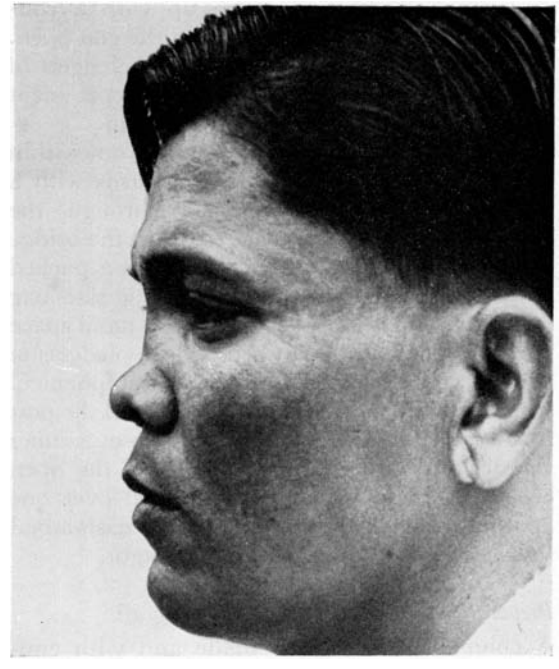


FIG. 6*a*.

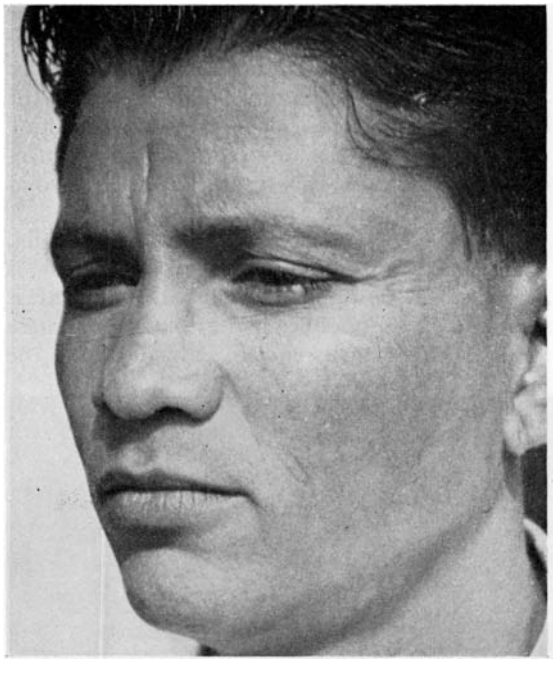


FIG. 7. 1 year after operation, showing partial absorption of crest graft.

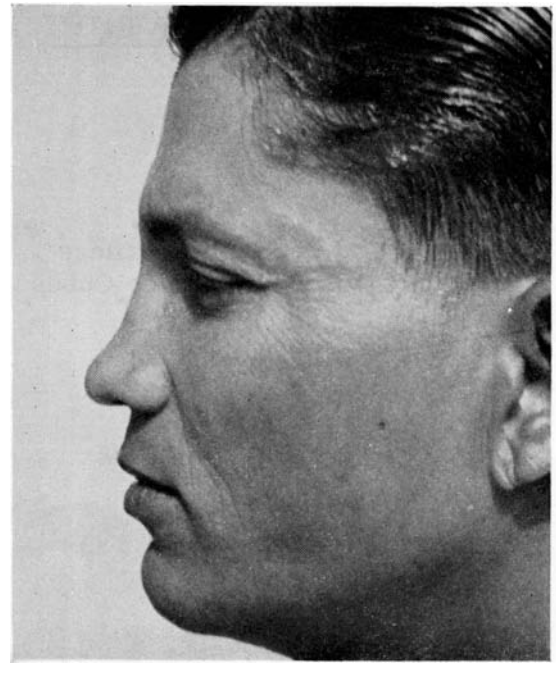


FIG. 7*a*.

bigger crest graft. The columellar incision is closed with fine Nylon sutures.

The anterior nares are packed with further pledgets of cotton wool squeezed out in paraffin and chloramphenicol suspension. This helps to push the skin bag more firmly in place, but care must be taken to see that these pledgets do not slip anteriorly into the space between the skin graft and undersurface of the nose.

Post Operative management

A small piece of gauze is strapped over the anterior nares and changed daily.

Penicillin 500,000 units and Streptomycin 0.5 gm. are given, I.M.I. twice a day for 5 days.

Between the 5th and the 7th day, if there is any discharge, the packing in the anterior nares is changed and fresh pledgets of cotton wool squeezed out in chloramphenicol and paraffin suspension are introduced.

Between the 10th and 12th day, according to the presence of discharge, the packing in the anterior nares is again removed and the presenting part of the skin bag is perforated. The enclosed packing is then removed and the posterior wall of the skin bag is perforated to establish an airway. The graft is usually found to have taken over the cartilage chips, and if by chance any cartilage chips are still exposed, they will be seen to be embedded firmly in a matrix of clot and granulation tissue resembling apple jelly. The cavity is lightly packed with ribbon gauze also squeezed out in chloramphenicol and paraffin suspension. This pack is removed after three or four days and any loose bits of skin graft are trimmed away. From then onwards the patient is asked to hold some normal saline in the cup of his hands three times a day and to inhale it to remove any crusts and secretions which may accumulate.

RESULTS

Thirty-one cases have been operated on to date and the immediate results in all have been good. The end results at follow up have also been good except in the few cases with late complications mentioned below.

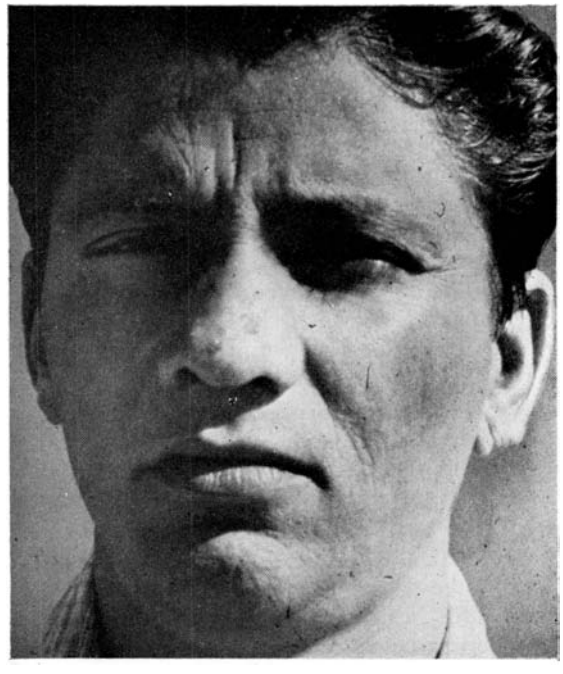


FIG. 8.

FIG. 8*a*.

After second revision operation.

Complications

The following complications have occurred:

A. Early –

(i) Non taking of the skin graft – one patient. A fresh graft bag was inserted during the second week after operation.

B. Late –

(i) Narrowing of the airway – four patients. In these cases it has been necessary to excise a shelf of cartilage and mucous membrane which caused narrowing of the opening between the nares and nasal cavity.

(ii) Complete absorption of the bone graft – two patients.
This has occurred in two patients and they have needed new bone and cartilage grafts and epithelial lining.

(iii) Partial absorption of the bone graft – three patients.
This has occurred in three patients. In one a new graft has been inserted and in one case the complete operation has been repeated.

SUMMARY

A new operation for reconstruction of the nose devised by the late Dr N. F. Cockett is described. After freeing the nose from the underlying bone through a naso-labial sulcus incision the upper part of the resulting cavity is filled with minute cartilage chips and the lower part with a skin graft bag as in a posterior nasal inlay. After closing the incision in the naso-labial sulcus a crest and columellar bone graft are inserted through a columellar incision.

ACKNOWLEDGEMENTS

I must express my thanks to the late Dr Norman Cockett who worked out the details of this operation, and also Dr Hebbar of Palghat, who has made the bone graft introducer.

REFERENCE

ANTIA (1963). *Ann. Roy. Coll. Surg. Engl.*, **32,** 71.

Abstracts

1. **Vaccination Against Experimental Infection with Mycobacterium leprae,** by CHARLES C. SHEPARD. *Am. J. of Epid.* 1965, **81,** 2, 150–163.

There was no evidence of post-infection immunity in experimental infections of mice with *Mycobacterium leprae.* Mice bearing infections with ten or more *M. leprae* in one rear foot pad were just as susceptible as uninoculated controls to infection in the other rear foot pad.

Several Mycobacterial species were tried as heat-killed intraperitoneal vaccines against *M. leprae* infections of mice and compared to living BCG. Tubercle bacilli gave the most protection, but there was evidence of moderate immunity with *M. marinum,* the QT isolate (a member of Runyon's group III), *M. lepraemurium,* and *M. ulcerans.* Living BCG gave the best results.

BCG given in a small dose into the foot pad to be challenged gave a high level of immunity in one experiment, but was not very effective in another.

The intravenous route was the most favourable one for BCG. The intracutaneous injection gave better protection than the intraperitoneal. The subcutaneous route seemed poorest.

When the bacilli were incorporated into Freund's adjuvant their subcutaneous immunogenicity was increased. Repetition of intracutaneous vaccine increased the protection.

The smallest dose of BCG tried intracutaneously was 1 x 10 bacilli and it gave clear protection. Increasing doses up to 5 x 10 gave increasing protection. Fresh Danish BCG vaccine in standard concentration was given in a dose of 0.01 ml intracutaneously (about 1.5 x 10 bacilli), and found to give clear protection.

2. **Lactate Dehydrogenase Activity in Mouse Liver Infected with Mycobacterium lepraemurium,** by P. C. WONG, MELANIE CHEN, GRACE CHUN TIE, and L. MA, of the Dept. of Path. & Bact. and Dept. of Chemistry, Chinese University of Hong Kong, *Jour. of Trop. Med and Hygiene,* May 1965, **68,** 5, p. 110–112.

The authors report that a survey of the literature shows that enzyme studies in leprosy have been very little studied. They found that the lactate dehydrogenase is higher in the liver tissue of mice after the fifth month of infection with living *Myco. lepraemurium* as compared with mice inoculated with the inactivated bacillus. They think that this change is probably associated with degeneration of the liver caused by the bacillus, and note that the drug Suramin, which enhances infection by the bacillus in mice, has little effect on the enzyme level.

3. **Effect of Cyclophosphamide and of RO 4-6467 on Leprosy,** by E. J. SCHULZ and G. FALKSON is a letter to the Editor of the *Lancet* referring to their first report on this matter p. 1138, *Lancet,* **2.**

The report was of suppression of acute reactions in five out of eight patients with leprosy who were treated with large doses of intravenous cyclophosphamide. They had found that erythema nodosum (ENL) occurred in 32 per cent of their patients with lepromatous and borderline leprosy, usually about 16 months of the initiation of treatment with dapsone. They found that this reaction is difficult to control, and even under long-term corticosteroid treatment may persist for years.

The authors report that they have now given a further nine patients with ENL small doses of oral cyclophosphamide (100 mgm. daily for from 98 to 146 days) and in none was there any significant improvement.

They also gave RO 4–6467 to six patients with ENL in a dosage of 50 mgm. daily by mouth, the total dosage varying from 17.85 g. to 37.8 g. Prednisone was given, as well as the basic anti-leprosy treatment. The latter was also given. No significant improvement was noted in any case. The authors conclude that low oral doses of cyclophosphamide and of RO 4–6467 are ineffective in controlling ENL.

4. **Tratamiento de los Estados Reaccionales en la Lepra y en la Oncocercosis (Treatment of Reactional states in leprosy and in Onchocerciasia),** M. SALAZAR MALLÉN, *Gaceta Médica de México* 94, 10, 972–979, Oct. 1964.

This reports on investigation carried out in Mexico under the Dept. of Public Health. The author comments that diethylcarbamazine (Hetrazán) has not found general acceptance for use in onococerciasis because of severe reactions. The author finds that this therapeutic shock called Mazzotti's reaction has a toxic nature and results from the release of serotonin. There is increased serotonin in the jugular blood in the early part of the reaction associated with erythema and itching. The late reaction of tissue destruction, associated with oedema, fever, malaise, and the appearance of C-reactive protein.

Methysergide has been used with success to avoid or diminish the skin symptoms, and corticosteroids (triamcinolong and indomethacin) to control the late reaction.

In leprosy sulphone-treated as well as untreated patients have acute reactions with arthritis, erythema, and fever. Some have purpuric lesions ending up in necrosis. In these reacting patients corticosteroids cannot be recommended because of a rebound phenomenon which is much worse than the reaction itself. The author found in his 14 lepromatous patients there were six who had Lucio type, and all 14 showed *Myco leprae* in the white cells of the blood, as well as C-reactive protein in the blood serum. Indomethacin in doses of 5 mgm. of body weight reduced or abolished the arthralgia and general symptoms, without affecting the erythema or the purpuric spots. When triamcinolone in doses of 1 to 2 mgm. were injected under the lesions the purpuric spots rapidly diminished without necrosis.

The use of DDS was continued throughout in all patients without untoward results. The reaction did not seem resulted from the use of chemotherapy.

Lep. Rev. (1965) **36,** 4, 223/234

Report of Field Trip—India, Vietnam, Philippine Islands and Okinawa

O. W. HASSELBLAD, M.D., PRESIDENT
28th December, 1964 *to* 23*rd February*, 1965

American Leprosy Missions, Inc., 297 *Park Avenue South, New York, N.Y.* 10010

1. BOMBAY, INDIA

One of the main reasons for visiting Bombay was not only to observe and evaluate the Nerve Lesion Research Project carried on at the J. J. Group of Hospitals under the direction of Dr N. H. Antia, plastic surgeon, and Dr D. K. Dastur, a neuropathologist, but also to see as much as possible of rehabilitation programmes for disabilities caused by other diseases. During my week there (December 30 to January 6) I had the opportunity of visiting every leprosy treatment and rehabilitation programme in the Bombay area. And in addition I saw many of the rehabilitation programmes being carried on for other disabled people. Following are brief descriptions of the places and projects visited and my comments and recommendations concerning them.

(a) *J. J. Hospital Group.* At this outstanding hospital centre where I made several visits with Dr Antia and Dr Dastur there are three projects under way in the Plastic Surgery Units: Research on Nerve Lesions in Leprosy, Rehabilitation in Leprosy and Burns, and the Development of Prosthetics for Leprosy and Other Disabilities. These projects are supported by grants from the Vocational Rehabilitation Administration. I was given every facility to observe all the various details of the nerve lesions research project, and was interested to watch a nerve dissection in which Dr Antia carried dissection of the ulnar nerve from high in the arm down to its finest terminal branch in the hand. He also fully dissected the median nerve. Wherever there were attachments of the nerve passing through tunnels or fibrous bands, either anatomical or pathological, these were freed. Wherever any nerve lesion was found the sheath was laid open carefully, avoiding any displacement of the nerve or interfering with the blood circulation of the sheath itself. Dr Dastur gave me some interesting domonstrations of pathological sections and slides. And I was particularly interested in the work of Dr James Smith of New York City because American Leprosy Missions had provided the camera equipment used to photograph nerve lesions and dissections, thus making a permanent record for teaching purposes. He demonstrated by the use of the diploscope in actual surgical procedures as well as on autopsy material that circulation to the nerve sheath is all important and must be preserved at any cost. Where indicated, biopsies were taken from the nerve but never when such a biopsy would deprive a viable nerve of its function. Electromyographic studies were done on all the nerves and their fine terminal branches in order to determine the conduction function of the nerve and to trace pathological origins of damaged nerves.

In my visit to the project on causes of burns, I was interested to learn that many of the burns occurring in women stemmed from attempts at suicide.

Dr Antia's plastic operation on the nose, which I observed one morning, used a plastic prosthetic device for restoring a nose depressed by leprosy. This technique was demonstrated in the film made by Dr Paul Brand and Dr N. H. Antia.

Some comments and recommendations:

1. Excellent progress has been made on the Nerve Lesion Project, the results of which, I believe, will be of far reaching significance in the prevention and treatment of deformity in leprosy.
2. In a talk with Professor Choksi, of the Tata Foundation and later with Dr D. V. Virkar, Dean of Grant Medical College and J. J. Hospitals Unit, I pointed out an obvious need for a project co-ordinator for all the programmes under Dr Antia. Both Dr Antia and Dr Dastur have to give too much time to administrative work. If Professor Choksi and Dr Virkar can find a suitable administrator, I believe it would be a valuable contribution for ALM help finance his support.

3. American Leprosy Missions should also provide such basic equipment as shelves and storage equipment, tables and furniture, the lack of which is a serious detriment in Dr Dastur's department.

4. Mr H. D. Pavri, occupational therapist at J. J. Hospital would benefit greatly from a study grant to gain experience abroad.

(b) *Kondhwa Leprosy Hospital.* With Dr N. J. Bandorawalla, Dr J. M. Mehta and other members of the Poona District Leprosy Committee, I spent a day of observation and discussion at this excellent treatment centre near the city of Poona. Following are some general comments and recommendations:

1. Hospital facilities are fine and Dr Antia has an active surgical programme.

2. Physiotherapist and other workers are well suited to the work and take great interest in it. Canadian nurse, Miss Shirley MacLean, who was recruited with Wyva Hasselblad's help, is making a significant contribution. A study grant for Mr W. Jennings, the physiotherapist, would be a valuable aid to his work.

3. Chicken farm and textile manufacturing units are excellent, but seem to be designed to support the hospital community rather than provide patients with skills

they can use to achieve economic and social stability when they return to their home communities.

4. In a discussion with the Committee on the VRA project, 'Research in Methods of Rehabilitation for Rural Communities', I made the following points:

(i) There doesn't seem to be any real link between what is being done at the centre and actually helping people to get established after their discharge.

(ii) Rural people must be helped where they are. Even a temporary dislocation by bringing them into a so-called rehabilitation centre will be a further dislocation and handicap.

(iii) The stigma associated with any centre identified with leprosy also works against effective social rehabilitation.

(iv) Wyva Hasselblad's report on her preliminary pilot study of the need for a rehabilitation project among rural patients showed that 86 per cent of the patients were living with their families, but that the great majority were already suffering some kind of social and economic dislocation. Any rehabilitation project for these people, therefore, should be designed not only to maintain what security they already have, but to discover ways by which they can regain real stability in the community.

(v) An effort should be made to find the proper investigating officer to carry out the rural rehabilitation project.

(c) *Workshop for Leprosy Patients.* This is a projected programme for outpatients in the Bombay area which grew out of a study of one thousand of these patients by a social worker to discover their economic needs. The need for such a workshop was based on a rigid and rather arbitrary rule that lepromatous patients must be under treatment for a specified time of five to ten years, during which time they should not associate with other people. In a number of discussions of this proposal I made the following points:

1. The premise itself is a false one, based upon a questionable idea of infectivity. It is now generally agreed that the danger of infectivity is likely to be reduced by early treatment, and the longer a patient is under treatment the less likely he is to be infective. Basis for the workshop should not be 'infectivity', but needs of the patients, whether infectious or not.

2. The project should not be a leprosy project *per se.* It should not be tied in with any leprosy organization or located at a known leprosy hospital such as the Acworth Leprosarium. One of the greatest values of Dr Antia's projects is that the workers are not in the strict sense, leprologists. It is thus being demonstrated that leprosy belongs in the mainstream of medical and scientific concerns. This emphasis should be carried over also into the field of rehabilitation.

3. The project should have an independent board of management to maintain control over its purpose and function.

4. Its main purpose should be to provide a means of livelihood for patients under treatment to keep them from becoming socially and economically dislocated.

5. An offer by Mr Chandra Kant Garawa, a plastics manufacturer, to help establish a paint brush factory in connection with the workshop project would be an excellent start. He was prepared to give technical guidance and handle the marketing of the products.

(d) *Acworth Leprosarium.* Dr N. Figueredo, superintendent of this large leprosy hospital runs eight other treatment centres in the Bombay area. About 10,000 new cases are discovered in Bombay in a year. Patients' workshops at Acworth are used almost entirely in helping to maintain the institution, and there is no real vocational training to prepare patients for the outside world.

(e) *Chembur Leprosy Beggars Home.* This is a place entirely for beggars who are taken off the streets and committed by law to the home. Dr Antia visits regularly, has provided a physiotherapist and takes those who need reparative surgery to the J. J. Hospital, and does what he can in the way of rehabilitation.

(f) *Phansa – Tata Agricultural and Rural Training Centre for the Blind.* Dr B. D. Pallonji, employment and placement officer for the National Association for the Blind, accompanied me to visit this project which is supported by the Vocational Rehabilitation Administration. It is designed to train blind boys in agricultural work, including crop planting, horticulture, poultry and cattle farming. At the very interesting Crop Museum, where a great number of crops are grown, the boys are taught to identify the different varieties by touch. Today nearly fifty boys have become self-supporting in all parts of India. The rehabilitation programme includes a placement officer to prepare the way for the boys' return to their homes, the purchase of land, when necessary, by the government, provision of tools, and an excellent follow-up service.

Mr Rustom Doctor, a well-to-do farmer and chairman of the Phansa Committee, showed us through the project for the blind boys, invited me to visit a small leprosy rehabilitation centre he had established in his own area, caring for 20 residents and 180 outpatients. The staff, including the superintendent, are all former patients. I think American Leprosy Missions should help this man who has taken the initiative in caring for the people in his locality by giving a grant to provide medicines and other necessities.

(g) *King Edward Memorial Infirmary.* Under the direction of the Salvation Army, this government project is run in connection with a beggars camp where those found begging on the streets have been sentenced to one to five years. It is designed to prepare these beggars, all of whom are disabled by various diseases, amputations, etc., for useful employment after they have served their sentences. It consists primarily of job work given from factories and returned to factories for marketing, such as bookbinding, carding, safety pins, plastic work and printing. After their release, efforts are made to find employment for these rehabilitated former beggars.

(h) *Tata Cancer Hospital and Rehabilitation Centre.* This project, which I visited with Mrs Kamala Nimbkar, Editor of *The Journal of Rehabilitation in Asia*, not only provides useful occupational therapy for patients under treatment, but also employs families of cancer patients. Because of the long periods of treatment, many families

accompany the patient and often find it difficult to support themselves.

(i) *Workshop for the Blind.* In this beautiful new building in the city, blind men undergo a one or two year training period in a number of skills. Though they operate lathes, drills, electrical power saws and other complicated and dangerous machinery, the provision of safeguards and good training have prevented any injuries. They also assemble such things as car headlights with 17 components, radio parts and other very detailed work.

I addressed a group of 30 journalists from all over India who were visiting the workshop under the sponsorship of the United States Information Service and had a good opportunity to discuss the problems of leprosy in relation to the total rehabilitation programmes.

(j) *Fellowship of the Handicapped.* This new building for disabled men, was built by a remarkable woman, Mrs F. Ismail, whose achievements in rehabilitation were motivated by her own polio-afflicted daughter. In caring for her daughter, who now lives a completely normal life, Mrs Ismail learned all the techniques she now uses in developing projects for other disabled. Here some 140 disabled men are taught skills and settled in open industry with follow-up care and guidance.

(k) *Rehabilitation Centre for 'Toddy Tappers'.* Former manufacturers of the very potent palm brew, displaced by prohibition, are being helped in this government rehabilitation centre to make non-alcoholic products out of palm trees. These include an unfermented juice called *neera*, sugar, vinegar, syrup; and from the fibre and bark such things as rope, baskets and other materials.

During my visit I had many interesting and fruitful observations with outstanding community leaders. In addition to those already noted, to whom I am indeed grateful for the time they gave, I should also like to mention Dr Sharat C. Desai, dermatologist and professor at the King Edward Memorial Hospital Medical School who has integrated leprosy in his department; Mr M. S. Mehendale, educational officer working with the Gandhi Memorial Leprosy Foundation, whose job is to educate medical practitioners, public leaders, educators and the average citizen about the facts of leprosy. I was most appreciative of the opportunity to discuss leprosy problems, especially those of rural rehabilitation, with Sri Shantilal Shah, Government of Maharashtra Health Minister, who spoke highly of my daughter Wyva's work at Kondhwa. Sri Shah's knowledge of leprosy was very great and he offered co-operation and financial help for any projects that we cared to submit to him.

I was grateful for the many opportunities during my stay in the Bombay area to visit various rehabilitation projects for other than leprosy-caused disabilities. It is quite clear that in the special problems of rehabilitation in leprosy, there is a great deal to be learned from what is happening in the rehabilitation of people with disabilities arising from other causes.

2. WARDHA – INDIA

This town of 25,000 is the headquarters of the Gandhi Memorial Leprosy Foundation which was established in 1951 under the direction of Dr R. V. Wardekar as an entirely new approach to the problem of treating the great number of patients in India – a number too vast to be cared for in institutions.

The introduction of the sulfone drugs as a new and effective remedy for leprosy made it possible for the first time to treat the disease on a mass scale.

The object of the Foundation's programme was not only to try to carry out widespread treatment but also to establish training centres for paramedical workers.

Leprosy control units and two control clinics have been opened at ten places in endemic areas. The programme covers 362 villages with a population of more than two million, and includes annual surveys, educational work and medical treatment.

Under the direction of one medical officer and one paramedical worker, each unit covers a population of about 25,000 people within a radius of approximately ten square miles. They are located where there is an *estimated incidence of 30 patients per 1,000 population.* Because of Dr Wardekar's experience in these units, he developed the so-called survey, educational and treatment (SET) units which have been recommended to the government as the accepted method of leprosy control.

The first unit was started in 1951 at Sevagram near the ashram where Gandhi spent most of his working years in India, and the last unit was set up in 1955.

Connected with the control units are the central laboratory at Wardha and the paramedical workers training centre at Chilakalapalli, which not only serves as a model training centre but also as a source of supply of paramedical workers to a number of state governments and non-official agencies.

The Foundation has also undertaken at Chilakalapalli an experiment on the prophylactic control of leprosy. In a given circumscribed area all people under 25 are given DDS and treated for six months with the regular dosage, then put on a maintenance dose for an observation period. The experiment, which started in April 1963 with a control group of untreated healthy people, will have to be carried on for seven years or so to know precisely whether the prevalence of leprosy is appreciably less in the treated group.

Following are some general observations and comments on this pioneer mass treatment campaign:

1. There is evidence that all patients have been registered in that area by constantly surveying the population and following up every contact.

2. There has been quite a reduction in leprosy incidence. Although the lepromatous rate has come down considerably, a hard core of cases still remain. Since new cases are found regularly, one wonders whether the lepromatous case is the only source of infection.

3. Statistics are so well kept, with all kinds of counter-checks, that it will be possible to determine by careful evaluation and statistics how effective is this method of control.

4. For the last two years education has been substituted for surveys in one or two units, to find out if educating the public will bring in as many cases for treatment as house to house surveys. If effective, this method would have the obvious advantages of saving time and expense and also of awakening community responsibility for seeing that all cases are treated. The educational programme,

which uses slides and pictures illustrating all types of leprosy, how it originates, how it spreads and how it can be controlled, gives a realistic and hopeful understanding of the disease.

5. If the methods used by Dr Wardekar in the leprosy control units can be instituted on a large enough scale, it seems quite clear that rehabilitation programmes will be unnecessary, because people who are treated at home and stay within the security of family and community, do not need rehabilitation.

The two days I spent with Dr Wardekar, during which I visited the Central Laboratory at Wardha and the control unit at Sevagram, were meaningful and informative. A scientist with a great understanding of public health measures and of epidemiology, Dr Wardekar has the confidence of the government and will probably, more than any other man, influence the future of leprosy control in India.

3. KARIGIRI, INDIA

Since my visit to the Wm. Jay Schieffelin Leprosy Research Sanatorium in 1962, there have been many developments in buildings and staff. The lovely new chapel built by the Mission to Lepers has given a real sense of unity to the work and serves as a centre for the entire hospital community. There are new staff quarters and two new wards, one a women's ward, built by ALM and The Mission to Lepers, and the other built by the Swedish Red Cross for epidemiological studies. The Swedish Red Cross is also building its own administrative building.

New staff members include Dr A. B. A. Karat, B.SC., M.B., M.R.C.P. (Lond.), M.R.C.P. (Edinburgh), Consultant Physician, who will head the medical department and do research and Dr (Mrs) A. B. A. Karat, F.R.C.S., Chief Surgeon, who heads the surgical unit. There is increasing co-operation between the Christian Medical College in Vellore and Schieffelin Sanatorium. Dr and Mrs Karat have honorary staff appointments at Vellore Christian Medical College and Dr C. K. Job, B.SC., B.B.S., M.D., is Professor of Pathology there. Dr A. J. Selvapandian, B.SC., M.B., M.S., Dr E. P. Fritschi, F.R.C.S., and others at Vellore continue as consultants at Karigiri and several members of the Vellore staff are aiding in various research programmes.

During my stay the new women's ward was officially opened, and the ceremonies attracted a large audience. Dr Reidaman, pastor of this parish led the worship and prayers. Dr Job spoke about the contribution of ALM to Karigiri, pointing out that ALM provided the original capital to launch the work and has continued to provide, in co-operation with The Mission to Lepers, the means for what progress has been made. I spoke briefly and cut the ribbon opening the ward.

Following are some additional observations and comments:

1. A particular need at Karigiri is for an epidemiologist with a good background of training and experience.
2. There is also a need for much more co-ordination in research programmes carried on in various centres. Because of the lack of sufficient contact, there is probably a great deal of unnecessary duplication. A cross-fertilization of ideas between research institutions would be invaluable.
3. Karigiri, for example, should have a special budget for research workers to visit other areas.

4. VELLORE, INDIA

In my visits to the Christian Medical College it was encouraging to see how fully leprosy work has been integrated into the Orthopaedics Department, of which Dr A. J. Selvapandian is head, in the Orthopaedic Ward and in the new Department of Physical Medicine and Rehabilitation headed by Dr Mary Verghese, M.B.B.S. and Member of American Board of Physical Medicine, which has introduced a whole new concept of rehabilitation.

In the Hand Research Unit, I discussed with Dr W. M. Lennox, B.SC., M.B., F.R.C.S. (Eng.), F.R.C.S. (Edin.), his significant new research in skin grafting. For the last two years Dr Lennox has done surgery at Vellore and Karigiri, and has set up surgical programmes in centres surrounding Vellore. His skin grafting research involves transferring areas of skin from one part of the hand which has retained sensation to another, thus restoring a trigger area of sensitivity.

5. RANIPET, INDIA

Here, too, the integration of leprosy control into a widespread public health scheme and into the work of the well-known Scudder Memorial Hospital is impressive and significant to the future of leprosy control in India. Dr Julius Savarirayan, B.A., M.B.B.S., director of Scudder Memorial, has undertaken the control of leprosy in an entire taluk, where he has direct responsibility for over 10,000 leprosy patients. In addition, a ward has been built on the general hospital compound for the care of leprosy patients with special complications. Dr Frank L. Zwemer, M.D., with the help of Dr Lennox of Karigiri and Vellore, has set up an excellent surgery programme.

6. MALAVANTHANGAL, INDIA
(Kasturba Kushta Nivaran Nilayam)

The leprosy control unit adopted by the Hind Kusht Nivaran Sangh is of special interest because the treatment and control aspect of the programme is balanced with a centre providing facilities to care for special complications, for the partially and totally disabled. In the centre a good vocational programme gives needed training for self-support. Selected patients from the control villages are brought in for two or three weeks at a time for occupational therapy and education in protecting their hands, etc.

7. MUTTATHUR, INDIA

A new hospital unit was built here recently by American Leprosy Missions and The Mission to Lepers. Related to the Reformed Church in America the centre also has a control area with paramedical workers. The director is Dr Kamala H. Lazarus, L.M.P., whose husband, Rev. Henry Lazarus, B.A., B.D., S.T.M., is the head of an extensive Christian programme under the Church of South India. Though still in its early development this significant unit has the support of government, the Hind Kusht Nivaran Sangh, and the British Leprosy Relief Association, and deserves the backing of all Christian organizations.

8. WANDIWASH, INDIA

With Dr (Mrs) S. Ponniah, M.D., B.S., and Dr M. D. Graham, I visited two roadside clinics near this centre, and was again impressed with the vast number of patients reached with the help of trained paramedical workers. The new hospital is now completed but staff quarters are still needed. I regret that this work has not had the encouragement and support it merits.

9. KATPADI, INDIA

The modern industrial plant built by the Swedish Red Cross and employing 50 former leprosy patients as well as those handicapped by various causes, is a pioneer project in a sheltered type of industry. Completely self-supporting, the modern, well-run workshop meets competition from other industrial plants, proving that its workers are capable of first rate production. The plant is part of the comprehensive domiciliary treatment programme the Swedish Red Cross is administering out of Karigiri.

10. CHESHIRE HOME, VELLORE, INDIA

A home established by the internationally known Cheshire Foundation cares for the chronically ill and those who cannot be rehabilitated. About 25 severely handicapped people have attained a degree of self-support in a comfortable environment. The governing board of which Dr Selvapandian is a member, is made up of public-minded citizens who have a special concern for the handicapped. I believe that American Leprosy Missions should send a grant as a mark of encouragement to a facet of leprosy work which is still needed.

11. POLAMBAKKAM, INDIA

This famous pioneering control centre had its beginnings when Dr Robert G. Cochrane, M.D., F.R.C.P., D.T.M. and H., ALM's former medical advisor, started a programme of night segregation of leprosy patients in the area. Later taken over by Belgian workers, the centre covers an area of 50 square miles, with a population of 700,000 in 86 villages. As a result of careful surveys, there are now 20,000 patients under treatment. Three doctors, and a number of well-trained paramedical workers handle this tremendous caseload. In fact, the whole basis of the programme is the paramedical worker. Sub-centres are located at strategic villages so that patients won't have to walk long distances for treatment. A careful follow-up service checks on absenteeism.

Here rehabilitation really begins with diagnosis and the prevention of dislocation. The occupational therapy programme simply provides a means for temporary occupation while in the hospital for special complications.

Of the 20,000 under treatment, only 50 are totally dependent. Arrangements have been made to subsidize their care in the homes of relatives or friends, a method of custodial care which has been found far more effective and inexpensive than establishing a separate institution.

Another group of about 50 who are only partially disabled are cared for at The Home of the Beatitudes, where they do some work to the extent of their abilities.

An evaluation of the ten years of work at Polambakkam is now under way and will determine whether this kind of control programme is practical; and, if carried out on a national scale, could effect the incidence of leprosy.

I owe a debt of gratitude to Dr C. Vellut, who spent much time showing me the facilities of the central unit and going over with me the details of the widespread programme and its well-kept records.

12. CHINGLEPUT, INDIA

Accompanied by Dr Job of Karigiri, I visited the famed leprosy teaching and research centre, The Lady Willingdon Sanatorium established by the Indian government and directed by the well-known Indian leprologist, Dr Dharmendra. The Sanatorium, with its magnificent facilities and large administrative unit, undertakes research in many aspects of leprosy. Among the department heads whose work was particularly impressive are Dr C. G. S. Iyer, M.D. (Bom.), F.C.P.S. (Bom.), a neuropathologist who is head of the Research Division and the Pathology Department, and Dr P. Mohamed Ali, head of the Epidemiology Department, who directs the control programme and an experimental programme on the use of prophylaxis. In this experiment DDS is given to children of all contacts in a given area.

Dr Dharmendra, who has made a great contribution to the understanding of leprosy, expressed a high regard for the work at Karigiri, which he thinks is uniquely significant. This interest is most gratifying and should, by all means, be reciprocated by the Karigiri staff.

13. AMBUR, INDIA

Established more than 40 years ago by The Lutheran Church – Missouri Synod, the Ambur centre is known for its achievements in the control and treatment of tuberculosis. Dr Wolf Bulle, a member of ALM's Board of Directors, directed the centre for some years before he took his present post as medical secretary of the Missouri Synod. Though the hospital has for some time cared for leprosy outpatients in their regular clinic, a new and comprehensive leprosy control programme, similar to the T.B. programme, has been established under the direction of the present medical officer, Dr Johannes Pueschel. As a part of the domiciliary treatment programme of the Schieffelin Sanatorium, establishment of the new unit gives over-all leprosy control in the taluk for which Karigiri is responsible. Patients needing hospitalization and special care are treated in the Ambur General Hospital wards.

Here are some added comments:

1. The well-organized hospital at Ambur offers a well-balanced programme with all community needs taken into consideration.

2. It offers an excellent example of the involvement, not only with medical and surgical treatment of acute diseases, but also with the total public health problems of the community.

3. It demonstrates that a general hospital must care for all chronic diseases, including leprosy, that are highly endemic in the area.

14. MADRAS, INDIA

At the headquarters of the Hind Kusht Nivaran Sangh, I had the pleasure of meeting again its organizing secretary, Dr T. N. Jagadisan, with whom I served on the panel on

Educational and Social Aspects of Leprosy at the International Congress of Leprology in Rio de Janeiro in 1963.

A former leprosy patient himself, Dr Jagadisan was encouraged by Dr Cochrane to specialize in leprosy and has dedicated his life to the service of other victims through the Hind Kusht Nivaran Sangh. An intimate of Mahatma Gandhi, Dr Jagadisan has written a book about him and his relationship to leprosy work. It will be published shortly.

15. CALCUTTA, INDIA

During a few days stop-over in Calcutta, I met Dr Victor Das of the Mission to Lepers. I was grateful to Dr Das for coming from Purulia to discuss the many mutual problems of our two organizations. We discussed the question of aided versus owned work of The Mission to Lepers. Though owned-work must of necessity receive first attention, Dr Das does agree that aided-work must also be developed to the level of other programmes.

Dr Das has requested and strongly urged that I come again to India as soon as possible so that we might visit together some of the places where these come into focus.

I also visited a number of industrial projects in Calcutta which could set a pattern for sheltered workshops and rural programmes suitable for leprosy rehabilitation.

Since my projected trip to Jorhat was unavoidably cancelled, I was pleased that Revd M. Savino, superintendent of the Jorhat Christian Leprosy Hospital, came to Calcutta to report on recent progress made at my former mission station. The leprosarium, which has been beset with difficulties in the last few years, seems to be on the up-turn. Inpatients have been reduced to about 150 and outpatients increased to almost 700. Two mobile units take treatment to outlying centres every week. Many former patients have been resettled on to farming land and only a handful remain at the leprosarium for continuing custodial care. Most encouraging is the growing co-operation between the leprosy centre and the general hospital where cases are admitted for surgery.

VIET NAM

SAIGON, VIET NAM

It was a very special joy to be met at the airport here by my daughter, Marva, a nurse at the Evangelical Church Hospital in Nhatrang. We stayed with the Longacres, the Mennonite representatives in charge of the relief programme in Saigon, before journeying on to Nhatrang.

Excellent progress has been made in the Nhatrang mission hospital in terms of increased facilities and better arrangements for the outpatient clinic which treats hundreds of patients. There has also been an advance in the tuberculosis programme, which now gives regular care to 25 or more inpatients and many outpatients.

Most members of the hospital board are connected in some way with the Church of Christ in Viet Nam and some are from the Christian and Missionary Alliance Seminary nearby. It was reassuring to me to know that responsible men are watching the situation closely and keeping in touch with the Chief of the province. I confess to being worried about the distance of the hospital from town and its vulnerability to attack. But I trust in an all-loving God and my daughter's own judgment which she exercises without panic or fear.

After my return to Saigon, I visited the pastor of the International Church, formerly of White Plains, New York, who has developed a strong ministry in the city's international community, and an American woman, Mrs Manfull, who has become interested in leprosy work through an organization with the unfortunate name of Friends of the Lepers. The organization has succeeded in improving the conditions formerly existing at the government leprosarium. Mrs Manfull, whose husband is in the American Embassy is a good example of the American woman who uses her time and energy, while living in a foreign country for the public good.

I also had an interesting visit with Dr Le-Van-Thong, M.D., a Lt.-Colonel in the Vietnamese army, who runs the only rehabilitation centre in Viet Nam for disabled army veterans. It includes a prosthesis manufacturing shop, a vocational retraining programme for patients and also for the widows of military men. Expansion of its work to include disabilities from other causes would be a desirable development in this excellent project. Dr Thong also cares for some 100 crippled children in a Catholic institution just across the street from his workshop.

HISTORICAL BACKGROUND OF PHILIPPINE LEPROSY CONTROL PROGRAMME

Though leprosy doubtless existed in the Philippines long before the coming of the Spaniards, there is no record of any care given its victims until the latter part of the 16th century when a Franciscan missionary dedicated his life to leprosy service with the support of his church and occasional aid from the government. This humanitarian work, which consisted of providing shelter and other bare necessities, continued throughout the Spanish régime. During this period only two noteworthy actions have been recorded: a numerical survey of cases in Cebu by Lobres, a provincial health officer, and a royal decree in 1830 establishing three leprosy settlements in Manila, Cebu and Nueva Caceres. Only those in advanced stages, numbering not more than 400 or 500, were sent to these colonies. By the end of the Spanish-American War and the beginning of the American Army Occupation estimates of leprosy incidence in the Islands ranged from ten to thirty thousand.

Under the two-year (1898–1900) military government, according to Dr C. B. Lara, former head of Culion, 'thought was given to the need of (leprosy control) and since there was no other known control measure but segregation, long practiced in Norway and Hawaii, an isolated island was sought. A military board selected Cagayan de Sulu. The civil government (1901–1905) found it unsuitable and decided on Culion with its 13 neighbouring islands. Two names were prominent in this

connection: Professor Dean Worcester, Secretary of the Interior under Governor-General William Howard Taft; and Dr Victor Heiser, first Director of Health for the Philippines.' It was 1906 before construction of the leprosarium was completed, and in May of that year 365 patients were transferred from the settlement at Cebu to Culion, some 200 miles southwest of Manila.

In his book, *An American Doctor's Odyssey*, Dr Heiser says: 'When I became Director of Health of the Philippines I realized that one of my most important duties would be to isolate the lepers. I believed that isolation not only protected others from contracting leprosy, but was the most humane solution for the leper himself. Instead of being shunned and rebuffed by the world, he could have an opportunity to associate with others of his kind in pleasant relationship.'

In the light of our present day knowledge of leprosy, however, the rounding up of sick people, which was done in every province during the next six years by local officials and the police, often by force, was anything but humane. Act 1711, passed in 1907, providing for the 'apprehension, detection, segregation and treatment of lepers' aroused in some areas great resentment and resistance, yet health officials of that time knew no other way to control the disease.

When Major-General Leonard Wood was appointed Governor-General of the Philippines in 1921, he took an immediate interest in Culion and the whole problem of leprosy, visiting 'collecting stations' and investigating reported conditions of inhumane treatment in which patients were crowded in local jails, held many months, often a year without treatment, awaiting transport to Culion.

Greatly disturbed by these conditions, General Wood conceived the idea of establishing treatment stations throughout the islands so patients could get care near their homes while waiting to get to Culion, and where those in the early stages could remain for treatment without the necessity of being sent to the remote island leprosarium.

Because of his interest there was a marked change in Culion itself. The medical staff was greatly increased and in the twenties and early thirties the leprosarium became the leading centre for research.

LEONARD WOOD MEMORIAL

One action he took at the beginning of his administration held great significance for the whole future of leprosy treatment and research. In 1922 he persuaded a young and brilliant American pathologist, Dr H. H. Wade, then working with the Philippine Bureau of Science, to go to Culion as chief pathologist and acting chief physician. General Wood was so impressed by Wade's work at Culion that in 1927 he sent Mrs Wade to the United States to raise funds to create a research foundation for the study of leprosy and to construct appropriate facilities and a new leprosarium in Cebu.

As a result of Mrs Wade's successful fund-raising tour an American Committee for the Eradication of Leprosy was formed to aid the Philippine work. At General Wood's death in 1927 the name was changed to the Leonard Wood Memorial for the Eradication of Leprosy.

By 1930 the Cebu Leprosarium had been built with Leonard Wood Memorial Funds replacing the old collection of nipa huts in the city and was turned over to the government, with Dr Jose Rodriquez as its first director. Cebu was the first of the eight regional sanatoria proposed by General Wood. The last, the Central Luzon Sanatorium at Tala, was completed in 1938.

Another noteworthy event in the early thirties which would affect leprosy work all over the world was the International Round Table on Leprosy held by the Leonard Wood Memorial in Manila in January 1931. Out of this three-week meeting, attended by leprologists from all parts of the world and by representatives of the League of Nations, came the formation of The International Leprosy Association and its organ, *The International Journal of Leprosy*. Publication of this important journal began in 1933 with Dr Wade as editor.

THE PROTESTANT MINISTRY IN THE PHILIPPINES

Since Protestantism came to the Philippines only after the Spanish-American War, there were few if any Protestants among the first group of patients. Some years later pioneer missionary Dr George William Wright and Mrs Juana Coronel of the Presbyterian Mission of Manila started regular visits to Culion. By 1911 there were 30 Protestants who worshipped in a patient's hut. By 1915 the membership had doubled and had built a bamboo and nipa chapel. In 1917 a regular church was built by American Leprosy Missions, which had begun to support Dr Wright's chaplaincy service.

Another Presbyterian missionary who went to the Philippines at the beginning of the American occupation was Miss Elizabeth White. She began Bible classes among the patients in the old Spanish leprosy settlement, San Lazaro, just outside Manila, where she met a young Dane, Paul Frederick Jansen. After their marriage this young couple did pioneer work in the province of Batangas and Cebu, until they were told of the need at Culion by a young Philippine doctor. From 1922 until they were interned in Manila in 1944, the dedicated Jansens lived and served in a Protestant ministry at Culion with the financial support of American Leprosy Missions.

And as the regional leprosy hospitals were built during the thirties the ministry was extended to serve patients in them. Inter-denominational from the beginning, this ministry included construction of dormitories, wards, churches, schools for adults and teachers, self-help projects, the provision of food and clothing.

In 1935 Culion reached an all-time high of 6,997 patients. Ten years later, at the end of the Second World War, only 1,500 were left. In the first year of the war almost 2,000 patients left the island and many never reached their destinations. During the next three years half the remaining patients died from malaria and other diseases and from lack of food and medicines.

After the internment of the Jansens, the Rev. Ulpiano Evangelista took over the direction of the work. A nurse on Culion's medical staff for 20 years until he resigned in 1941 to assist the Jansens, Ulpiano Evangelista took special correspondence courses from the theological seminary at Manila and was ordained in 1942. He and his devoted wife, who still continue a full time ministry throughout all the Philippine leprosaria, developed at Culion a remarkable Protestant ministry which established churches in surrounding areas and created effective co-operative projects.

When the war ended a group of national Christian workers and missionaries of various denominations formed the Philippine Evangelical Leprosy Committee, which became the receiver and dispenser of funds from American Leprosy Missions. In 1963 the committee was incorporated as the Philippine Leprosy Mission, and undertook to support rehabilitation and research efforts as well as maintaining the strong spiritual ministry which now reaches some 900 Protestant patients. Working with the central committee in Manila are various local committees located in the centre of population nearest each sanatorium.

It was through this committee that American Leprosy Missions supplied sulfone drugs during a period in which the Philippine government did not have the means to reach all patients with the new medicine. Promin was being used at Culion, but on a very limited scale and for experimental purposes only. From 1947 through 1952, when the government started general treatment with sulfones, American Leprosy Missions supplied more than one million Diasone tablets to the Philippine Leprosy Committee to be administered through the Bureau of Public Welfare. According to an agreement between ALM's general secretary, Dr E. R. Kellersberger and government officials, half the amount was to be used for needy Protestant patients and the other half for Catholics and others. The provision of drugs to the Philippines was the first exception to American Leprosy Missions' policy of giving medicines only to non-governmental hospitals, and was made only because of the serious conditions in the Philippines after the war.

A MAJOR CHANGE OF POLICY IN GOVERNMENT LEPROSY CONTROL

In 1952 the hated segregation law was at long last revised (Republic Act 7530) to permit home isolation and treatment under approved conditions. This step marked the beginning of a major change of policy, a shift in emphasis from the leprosaria to field control work through systematic case finding and treatment. Later the Fifth Congress of the Republic of the Philippines passed the following:

Republic Act No. 4073

'AN ACT FURTHER LIBERALIZING THE TREATMENT OF LEPROSY BY AMENDING AND REPEALING CERTAIN SECTIONS OF THE REVISED ADMINISTRATIVE CODE.

Section 1. Sections one thousand fifty-eight and one thousand fifty-nine of the Revised Administrative Code, as amended, are further amended to read as follows:

Section 1058. PERSONS AFFLICTED WITH LEPROSY NOT BE SEGREGATED:

Except when certified by the Secretary of Health or his authorized representatives that the stage of the disease requires institutional treatment, no person afflicted with leprosy shall be confined in a leprosarium: Provided, that such person shall be treated in any government skin clinic, rural health unit or by a duly licensed physician.

Section 1059. CONFINEMENT AND TREATMENT IN SANATARIUM WHEN NECESSARY:

Whenever a person afflicted with leprosy shall have developed the disease to such a stage as to require institutional treatment and the leprosy officer shall so certify, the said person shall forthwith be sent to a government sanitarium and be treated therein until such time as the Secretary of Health or his authorized representative decides that institutional treatment is no longer necessary.

Section 2. Sections one thousand sixty to one thousand seventy-one, inclusive, of the same Code, as amended, are hereby repealed.

Section 3. This Act shall take effect upon its approval. Approved, June 18, 1964.'

Today there are three types of institutions used in a co-ordinated control programme throughout the Philippines: eight regional sanatoria; four stationary skin clinics (these stationary clinics operate in close co-operation with regional sanatoria); and ten travelling skin clinics.

In the travelling skin clinics, the first of which was started in 1930 by Dr Jose N. Rodriquez in Cebu, the actual treatment is administered by personnel of the rural health units. These units are under a municipal health officer and offer general training courses including leprology.

According to Dr Rodriquez, who served as Director of Disease Control until his retirement in 1963, the *per capita* cost of new cases discovered and treated in the travelling skin clinics is 75 pesos a year, and in the stationary skin clinics only 45 pesos.

REPORT ON SURVEY OF PHILIPPINE LEPROSARIA AND RECOMMENDATIONS FOR EXTENDING THE MINISTRY OF THE PHILIPPINE LEPROSY MISSION

INTRODUCTION

It is against the background of the history of the Philippine leprosy control programme and the recent changes in the world-wide approach to the leprosy problem that the Philippine Leprosy Mission must discover what service it can best give in the changing circumstances. This visit, my first to the Philippines, was undertaken specifically to discuss these problems with the Board of Directors of the Philippine Leprosy Mission following visits to each of the eight leprosaria in the islands. These visits were arranged through the kind offices of Dr Leandro B. Uyguanco, director of the Bureau of Disease Control of the Department of Health, who wrote to the hospital chiefs asking that I be given every facility and opportunity to study the work of the institutions. I would like to express here my gratitude for all the help given me and the many courtesies I received.

One of the gravest problems arising from the commendable change of emphasis in the government leprosy programme is that of educating the public to accept negative patients and convincing patients who can leave the leprosaria that it is to their benefit to do so.

A great many in the leprosaria are negative patients who have become accustomed to depend on the government for food, clothing, and maintenance. Some are positive cases who could just as well be treated in their home environments, but hate to leave the security of the institution. Some are disabled, but could be rehabilitated if proper medical, surgical and other rehabilitative techniques were available. Most difficult is the group in every leprosarium who have been isolated so long and are so physically debilitated there is no hope for rehabilitation. Many of these are now being sent to Culion which is apparently being transformed into a home for the completely dependent.

When positive cases or negative ones requiring continued treatment are discharged from the leprosaria they are referred to one of the skin clinics in the government's control programme for continuing treatment. While this new approach has as its basis, economic necessity, yet I like to think its chief motivation is to bring under control a greater number of patients for early diagnosis and treatment, and to prevent social and economic dislocation of sick people. This effective approach, with its noble purposes, is being followed today in many countries of the world.

I believe the primary objective of the Philippine Leprosy Mission should be to help the Philippine government implement its control programme. In the past we have provided an effective spiritual ministry to patients. It is now the feeling of many of the committee that a broader interpretation of the Christian witness would include helping patients to become integrated members of society and providing the social, vocational and economic factors necessary to this task.

Even before the incorporation of the Philippine committee, steps had begun toward this end. The most noteworthy was helping a former leprosy patient finish medical school and sending him to Karigiri for hand surgery and training in physiotherapy techniques. Dr Julio Pasion is now head of the Department of Physical Medicine and Rehabilitation at Tala, the only one of its kind in the Philippines. The committee also arranged and financed the training at Karigiri of Dr Jose N. Rivera, now doing surgery at Tala and working closely with Dr Pasion. And more recently Miss Judith Croot has been appointed full-time physiotherapist for the Philippine Leprosy Mission.

These instances mark a good beginning of an enlarged ministry. Changes will come slowly because some local pastors and committees find it difficult to realize the new opportunities of Christian service. Also the patients themselves must regain the qualities of dignity and self-respect and want to resume their rightful place in society.

RECOMMENDATIONS SUBMITTED TO THE PHILIPPINE LEPROSY MISSION

Though the world-wide changing pattern of leprosy work is based on scientific advances, neither the medical profession nor the general public are well prepared for these changes. The concept of rehabilitation, for example, is generally misunderstood, being widely regarded as something to be done after cure rather than a part of the total treatment and a preventive of social dislocation. And there is little awareness that the word 'cure' cannot really be applied until a patient is living a normal life in society.

In the light of these observations and because an effective Christian ministry must be conducted within the framework of scientific knowledge, I submit the following recommendations and suggested priorities:

I. *Central Luzon Sanatarium, Tala Province, Philippines*

(a) Dr Pasion and Dr Rivera should be sent to the Pan Pacific Conference on Rehabilitation in Tokyo in April, and also to Korea and Hong Kong for observation of leprosy work there.

(b) Miss Judith Croot, new physiotherapist for the Philippines, should be assigned to Tala as a primary base for development of rehabilitation and physiotherapy, though she would be available to other areas of need.

(c) Physiotherapy facilities already established under the direction of of Dr Pasion and Dr Rivera should be improved.

1. Physiotherapy, now regarded largely as an optional activity along with some occupational therapy, vocational training and recreational activity, should be integrated with the surgical programme and ordered by medical and surgical staff as a part of the general medical treatment.

2. The physiotherapy unit at Tala should be developed as a future training centre for paramedical workers.

3. Miss Croot's work should be closely related to the Department of Physical Medicine and also to the physiotherapy training course at the National Orthopaedic Hospital. An exchange of information and programme ideas will be helpful to both institutions.

II. *Mindano Central Sanitarium, Zamboanga City, Philippines*

(a) Careful consideration should be given to the possibility of supplying badly needed basic surgical instruments to this hospital, with the advice of the Division of Overseas Ministries and the Inter-Church Commission on Medical Care in the Philippines.

(b) Ways and means should be sought to support the existing but little used vocational training workshop and utilizing its facilities.

(c) Families ready to leave the hospital should be helped to resettle in their home communities, if possible. In cases of complete dislocation, the local church should be consulted and a joint effort made to help such families utilize what skills they have, or, if need be, to provide temporary financial help so they may become useful, contributing members of the community within the life of the Church.

III. *Eversley Childs Sanitarium, Cebu City, Philippines*

(a) Consideration should be given to a disability survey by Miss Croot of the great number of negative patients who have settled in a barrio in Cebu City and around the periphery of the Eversley Childs Leprosarium, to discover how many need surgical or non-surgical physical rehabilitation. These people are having an extremely

difficult time to survive and undoubtedly many of them are handicapped physically, socially and economically.

(b) The Philippine Leprosy Mission should finance a study trip to Karigiri for Dr Carlos Delgado of the Community Hospital in Cebu City. Dr Delgado has had excellent training in plastic, orthopaedic and hand surgery and would like to relate his experience and training to the special problems of leprosy. Dr Su, director of the Community Hospital, said that Dr Delgado and another qualified staff surgeon would be willing to undertake surgical treatment of negative leprosy patients with fees paid by Philippine Leprosy Mission. The importance of this programme would be to show that leprosy work can be integrated into general hospitals, and also that surgical treatment of leprosy disabilities is not only practical but urgently needed.

(c) Funds already made available to the Philippine Leprosy Mission for a rehabilitation project at Cebu should be allocated, at least in part, for a vocational programme, sponsored by the Protestant church, which would provide training facilities in such occupations as photography, sewing, etc. The programme should be open to all patients, regardless of religion. The whole purpose of the programme would be to train patients who would leave the hospital and resume a normal life in the community, not continue to live, on an income from their occupation, in the leprosarium.

IV. *Western Visayas Sanitarium, Iloilo, Philippines*

The Philippine Leprosy Mission should help build a ward for the treatment of plantar ulcers and surgical complications to be used by all patients at the institution. Wards now maintained by the Mission for use of Protestant patients might very well be used for the above purpose, if both government authorities and Protestant committee agree.

V. *Bicol Sanitarium, Sipocot, Philippines*

A strong effort should be made to continue the existing vocational programme, but it should be redirected toward resettlement in the community, if at all possible, near a church where a receptive climate could be created for negative patients.

VI. *Culion Sanitarium, Culion, Philippines*

(a) Consideration should be given to providing Dr N. Viado, in charge of patients in the Protestant wards, with a period of observation and study in centres in Korea, Hong Kong and, possibly, India.

(b) Churches that have been established in surrounding areas as a result of the outreach of the Culion Church should be utilized in a comprehensive programme of resettling the large number of families of negative patients now in the institution. The programme should include a careful study of the motivations, mental attitudes and vocational skills of the family members, and if necessary, temporary financial support should be given. It should be made clear that these subsidies are loans to be repaid.

ADDITIONAL GENERAL OBSERVATIONS AND RECOMMENDATIONS

I. Subject to the approval of Dr Uyguanco, American Leprosy Missions will provide subscriptions to technical magazines, useful reprints, and other literature to all doctors in the Philippine leprosy institutions.

II. Disseminating the facts about leprosy should be an obligation of the Philippine Leprosy Mission, particularly to its local committees. This can be done in various ways. Chairmen of local committees could attend the annual meeting at which an outstanding authority would discuss leprosy problems. And educational material could be distributed to the local committees. ALM will provide all such needed material.

III. Resettlement should be on an individual family, not a group, basis. Establishment of communities of patients or former patients should be avoided for obvious reasons.

IV. The establishment of rehabilitation centres, either inside or outside a leprosarium, should be avoided. Rather, what resources we have should go into rehabilitating individuals and individual families and supporting government projects. Even if the government programme is fully implemented it will be a matter of years before most patients will be treated in their own communities. Those who need rehabilitation are those now living in the institutions.

V. There is a great need for the development of educational materials in the Philippines. People with writing skills and those familiar with the subject should be enlisted in this programme. Background material can be supplied by American Leprosy Missions, and I would urge that whatever is published should be submitted to the ALM editorial staff to check for scientific accuracy. There are three basic types of literature needed:

1. Promotional literature to acquaint the church with the scope and programme of the Philippine Leprosy Mission.

2. Educational literature for the public regarding the facts of leprosy, the worldwide problem and the government's programme.

3. Educational literature for patients written in simple language and showing by use of illustrations what they themselves can do to prevent crippling and deformity.

VI. Co-operation of the Philippine Leprosy Mission in the annual observance of World Day for Leprosy Sufferers on the last Sunday of each January would be of immense educational value in the Philippines. Programme materials will be supplied by American Leprosy Missions.

VII. The role of Protestant pastors in government institutions needs to be re-evaluated.

(a) While they are pastors to Protestant patients who are members of their churches, these chaplains should remember they are called upon to be pastor to all patients and to the staff, and that they have a duty to co-operate with the staff as responsible officers participating in a total leprosy control programme.

(b) Pastors should try to avoid the development of static ingrown communities of Protestants. The patient should be made to understand that his stay in the institution is only temporary, and all activities and thought directed toward his return home.

(c) The Gospel given to patients should create an attitude of hopefulness and expectancy, and a determination not to let sickness separate them from normal living, nor to become dependent. It should give a sense of self-reliance, dignity and self-respect.

(d) Church educational programmes should not only contain the basic elements of the faith, but also matters of health, hygiene and how to prevent the disabling effects of leprosy.

(e) Pastors should have some knowledge of social work, and if possible get training in it. They should make the word of God relevant to the everyday needs of His people, not only while they are patients, but also so that they may be better prepared to live as normal, healthy members of a community.

(f) Former patients who have resettled in nearby communities are equally a pastor's concern. They need his help and guidance in meeting social, economic and vocational problems.

(g) There should be full co-operation with medical authorities, and confidence that they are acting in the best interests of their patients in accordance with scientific advances in knowledge of leprosy.

(h) The time has come for the churches in local communities to take over the support of the pastor, chaplain and church in each leprosaria. The church in the institution ministers to people of many churches and denominations who have come from scattered communities. These local churches should have a sense of responsibility for their members who are under treatment. I therefore recommend that American Leprosy Missions withdraw financial support to churches in the leprosaria over the next four years. This will be on a percentage basis and the support will be picked up by the local committees. This action is not only in harmony with the indigenous principles of the Life and Growth of the Church; it gives an opportunity to churches near hospitals and clinics to become involved in the needs of leprosy patients. I believe that American Leprosy Missions can give a more effective Christian witness by using its funds to serve the needs of all patients in an institution.

VIII. The Philippine Leprosy Mission should give serious consideration to creating a full-time office of General Secretary, with the following qualifications and responsibilities.

(a) He should have special administrative skills and authoritative knowledge of present-day leprosy management. This knowledge can be acquired by personal observation of work in other countries and by orientation from American Leprosy Missions and authorities in the field.

(b) He should co-ordinate activities of all local committees, and implement and carry out the programme of the Philippine Leprosy Mission.

(c) He should be responsible for creating the suggested literature programme, with the help of volunteer specialists. He might also create a library of audio visual aids which would be helpful in public education, in churches and even to doctors in the various leprosaria.

(d) He should serve as liaison officer with American Leprosy Missions.

In closing I would again emphasize that the future programme of the Philippine Leprosy Mission should be in harmony and compatible with the best known principles of the management of leprosy. In no way does this conflict with the primary responsibility of the Philippine Leprosy Mission to use this ministry as a means of communicating the Gospel of our Lord to those who have suffered not only physically but socially and economically.

OKINAWA

In 1927 a Japanese leprosy patient, Keiya Aoki, who had become a Christian under the influence of Miss Hannah Riddel, an Anglican missionary at the Kumamoto Leprosy Hospital in Kyushu, Japan, went as a lay missionary to the Ryuku Islands. He obtained land on the Island of Yagaji, off the northern coast of Motobu Peninsula and gradually collected about him a group of neglected and persecuted leprosy victims. This small Christian settlement formed the nucleus of the Airaku-En Leprosarium, which was taken over by the Japanese government in 1938, built into a model hospital of some 700 patients, and then almost completely wiped out during the bombing of Okinawa by Allied planes in 1944 and 1945.

At the end of World War II, when the American military government took over the administration of the Ryukyu Islands, the leprosarium was rebuilt and the patient body soon increased to almost 1,000. American Leprosy Missions, in addition to sending material gifts to the patients, also helped rebuild the interdenominational chapel which had been bombed by mistake.

Now under the jurisdiction of the United States Civil Administration of the Ryukyu Islands (USCAR), Airaku-en is the largest of the two leprosaria on the Ryukyus, with about 900 resident patients. Nansei-en in Miyako cares for about 300.

Before the war mission work in Okinawa was carried on primarily by the Episcopal church which still continues an outstanding ministry. Since then, however, various other mission groups have started work in the Ryukyu Islands, carrying on co-operative projects through the United Church of Christ in Okinawa and the Okinawa Interboard Committee.

Because of the increasing mission interest in Okinawa, as well as the presence of American military and civilian groups there, American Leprosy Missions is frequently queried about the leprosy problem in that area.

One of the main reasons for my brief stopover in the Ryukyus at the end of my field trip in Asia was to visit the two leprosaria and to get first hand information from workers on the spot.

I landed at Naha City and was met by Dr Paul Warner, Field Representative of the Okinawa Interboard Committee, Dr Tsuneo Inami, Medical Officer in Charge of the Airaku-en Leprosarium, the Rev. Luke Teruo Kimoto,

pastor of the Airaku-en Chapel, and Dr Jiro Minato, Japanese missionary surgeon to Okinawa.

Dr Inami, who accompanied me on all my visits and official calls, had visited ALM headquarters in 1964 when he was in this country to do graduate work in dermatology.

1. NANSEI-EN LEPROSARIUM, MIYAKO ISLAND

Under the direction of Dr Shinjo, this beautifully located institution with its splendid modern facilities, cares for about 300 patients. One aspect of the medical work which disturbed me, however, was the protective clothing and masks nurses were required to wear. Another disturbing element was three beautiful and imposing church buildings to serve only a handful of Christians.

In Hirara City, the nearest town, we visited the Rev. Takashi Shinjo, pastor of St James Episcopal Church and also of St Michael's Church at the leprosarium. In addition to his regular ministry in the two pastorates Mr Shinjo runs a sheltered workshop for the disabled, among whom are several former leprosy patients, and a kindergarten for children of the patients.

2. AIRAKU-EN LEPROSARIUM, YAGAJI ISLAND

Located near the city of Nago, Airaku-en incorporates most of the present day methods in the management of leprosy. An excellent staff includes Dr Minato, who has instituted a fine programme of reconstructive surgery. Other aspects of the well-balanced programme include good laboratory and X-ray facilities, and eye department and physiotherapy programme. One interesting feature, which I had never seen before, is a training course for student nurses. For two weeks in rotation a group of 12 comes to the leprosarium for orientation and actual work experience. This is an excellent method of educating not only the medical profession but also the public.

On Sunday I attended worship services at the very fine Episcopal church, whose pastor, Mr Kimoto, also serves a church in Yagaji Village.

An inspiring rehabilitation project carried on by the Episcopal Church is the Nago Folkcrafts Centre in Naha City. Under the direction of the Venerable William A. Hio of the Okinawa Mission of the Episcopal Church, this thriving industry offers vocational training and economic independence to many, including the handicapped and disabled.

Before I left Okinawa, in addition to visits with various government officials, I also had the pleasure of attending a monthly fellowship meeting of mission representatives at Naha.

Although the excellent government support of leprosy work in the Ryukyus makes unnecessary any direct involvement of American Leprosy Missions, I should like, however, to offer the following suggestions of possible supportive projects.

1. Co-operation in arranging physiotherapy training, and possibly training for an Okinawan nurse.

2. Provision of additional training for Dr Jiro Minato in reconstructive surgery.

3. Provision of technical films and literature for Airaku-en.

4. Support of the splendid work of the Okinawan Mission of the Episcopal Church and of the United Church of Christ in Okinawa.

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Letter to the Editor

Madrid,
29th June, 1965

Dear Sir,

Dr V. K. Loginov in a paper published in *Leprosy Review*, Vol. 35, No. 1, 1964, page 17, refers to an experiment carried out by Drs Guy Prieto and F. Contreras stating that the doctors had intentionally inoculated leprosy many times into a male nurse.

Doubtless, Dr Loginov had read on page 475 of the Memorial of the Sixth International Congress of Leprosy a paper entitled 'Immunity and Contagion in the Adult' in which we reported the attempts carried out by a nurse, but these were done at night and in secret without medical knowledge and were attempts at inoculating leprosy by various procedures.

We believe that such attempts demonstrate the difficulties with which contagion is attained in leprosy and it should be noted that these experiments under discussion were against our will, and it was necessary to give vigorous prohibition to the nurse against coming back to the clinics.

We agree with Dr Loginov that no doctor is authorised to do such inoculations and are not surprised at his reaction, but doubtless there has been misunderstanding and confusion by Dr Loginov because of defective translation of our language. It was perfectly clear in the original paper* that these inoculations were not under our control and approval.

Dr Felix Contreras.

* *Memoria del VI Congreso Internacional de Leprologia.*

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