LEPROSY REVIEW

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PRINCIPAL CONTENTS

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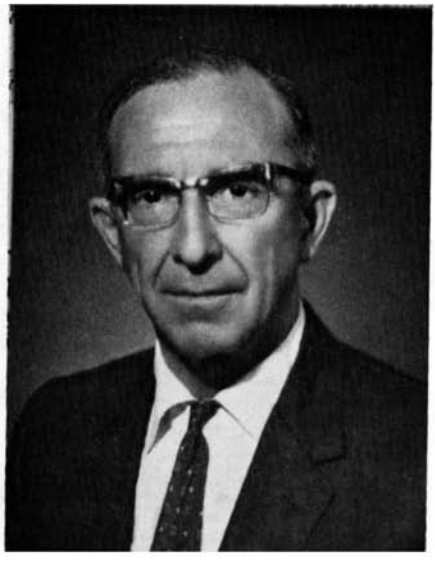
LEPROSY REVIEW

VOLUME XXXV NO. 3 APRIL 1964

Contents

Edited by DR. J. ROSS INNES, Medical Secretary of the British Leprosy Relief Association, 8 Portman Street, London, W.1, to whom all communications should be sent. The Association does not accept any responsibility for views expressed by writers. Printed by Eyre and Spottiswoode Limited, Her Majesty's Printers, at the Grosvenor Press, Portsmouth.

Editorial



DR. J. M. M. FERNÁNDEZ

I. DR. J. M. M. FERNÁNDEZ

It is not very often that we can record the likeness of a President of the International Leprosy Association. We are glad in this issue to give a photograph of DR. JOSÉ M. M. FERNÁNDEZ who was appointed President of ILA in September, 1963 at the 8th International Congress of Leprology at Rio de Janeiro. DR. FERNÁNDEZ holds the Chair of Dermatology at Rosario, Argentina, and is famous for his work in leprosy, especially in Pathology and Immunology. His name is attached to the early reaction when lepromin antigen is injected, viz. 'The Fernández Reaction'.

II. This issue contains a most interesting account by DR. A. E. WILDER SMITH of his work dealing with the relationship of some chemotherapeutic agents.

DR. M. G. CORCOS, in this issue, gives his study of two leprosy patients and puts forward the hypothesis that there are two antigens in each leprosy bacillus.

Some of the other papers deal with the results of damage in leprosy to peripheral nerves.

There is an interesting study by DR. REYES-JAVIER on the Isopathic Phenomenon of Sagher.

DR. O. K. SKINSNES gives the second of his careful accounts of oriental leprosy.

Metabolic Pathway and its Relationship to the Biological Activity of some Tuberculostatic and Leprostatic Agents

A. E. WILDER SMITH, B.SC., PH.D., F.R.I.C.,
Faculty of Medicine, Geneva

It is generally agreed that the metabolic pathway of a drug and its therapeutic activity are related[1] [2]. Some years ago[3] metabolic studies on the two tuberculostatics 4-pyridyl-oxadiazolone[5] and isoniazid, showed that both substances gave in the rat three identical metabolites. This fact was considered sufficient evidence to draw the conclusion that 4-pyridyl-oxadiazolone was metabolised in the body via isoniazid, which latter would be responsible for the tuberculostasis. The two drugs would be therefore clinically identical. Cross resistance studies using the two substances against various strains of *Mycobacterium tuberculosis* showed between 80–90 per cent cross resistance, confirming this view. Studies on 4-pyridyl-oxadiazolone[5] were therefore stopped, it being considered that it was simply another somewhat less active form of isoniazid.

Yet codeine, morphine and heroine are chemically closely related and show similar metabolic pathways in the body. But no one would think of applying them as clinically interchangeable. Their clinical and pharmacological spectra are different and well defined, even though their chemistry and metabolic pathways are so similar. Knowledge of the metabolic pathway is certainly useful, but a great deal of further data such as tissue and organ concentration, chemical stability towards enzymes, partition coefficients, etc., are necessary before attempting to pronounce on the likely clinical spectrum of new substance.

It is proposed here to describe one or two surprises we have experienced in research in the above field in the past few years.

1. If one subcultures H37 Rv in the presence of just sub-liminal doses of isoniazid, resistance develops rapidly as shown in Table I. After six subcultures the minimal inhibitory dose of isoniazid has risen from 1 : 40 million to 1 : 80 thousand.

But if 4-pyridyl-oxadiazolone is cultured under the same conditions against H37 Rv resistance emergence is much slower (Table I).

2. It seemed, therefore, that the two substances INH and 4-pyridyl-oxadiazolone were not absolutely biologically identical, at least *in vitro*, otherwise the resistance emergence rates would have been identical too. If their biological spectra are not absolutely identical, it was thought likely that, in the presence of 4-pyridyl-oxadiazolone, the resistance emergence rate towards INH would be modified. If the two substances possess exactly the same biological spectrum, a 1 : 1 mixture of INH and 4-pyridyl-oxadiazolone should show a resistance emergence rate

equal to that of INH alone. The pyridyl-oxadiazolone is ten times by weight less active than INH, so that one-tenth of the activity of the mixture will result from it and nine-tenths from isoniazid. Table II shows that 4-pyridyl-oxadiazolone does modify the resistance emergence rate to INH under *in vitro* experimental conditions and that therefore the two biological spectra are not totally superimposable.

3. The above finding is also applicable to other members of this series: p-amino-salicylic acid and p-amino-o-hydroxy-phenyl-1, 3, 4-oxadiazolone (WS 127) show the same activity weight for weight against H37 Rv and almost complete cross resistance. But when p-amino-salicylic acid and WS 127 in a 1 : 1 mixture are exposed to H37 Rv subcultures, the resistance emergence rate is lower than that given by p-amino-salicylic acid alone. See Tables III and IV.

It would seem, therefore, that, in this series of substances at least, cross resistance experiments do not always give exact information on the influence one mycobacteriostatic may have on another.

One of the great disappointments of recent years in the chemotherapy of leprosy has been the lack of leprostatic activity shown by isoniazid, in spite of its high tuberculostatic activity. On the basis of metabolic studies alone one would arrive at the conclusion that 4-pyridyl-oxadiazolone would also be inactive towards human leprosy. In fact, however, the oxadiazolone shows quite a high leprostatic activity, and also potentiates the leprostatic activity of Dapsone.[4] [5]

There are perhaps three possible explanations of this rather surprising fact:

1. The biological spectrum of pyridyl-oxadiazolone is not 100 per cent superimposable on that of isoniazid, and is leprostatic *per se*, whereas isoniazid does not possess leprostatic properties. One cannot settle this hypothesis either way satisfactorily until it has become possible to culture Mycobacterium leprae on a synthetic medium in the presence and in the absence of both substances.

2. Isoniazid possesses chemical properties different to those of 4-pyridyl-oxadiazolone. The former contains a primary and a tertiary amino-group, whereas the latter contains two amino and one tertiary amino-group, and is amphoteric. Isoniazid may therefore be transported in the organism by a different mechanism and route to that traversed by the oxadiazolone. This may mean that isoniazid may not reach the site of *Mycobacterium leprae* activity, whereas the pyridyl-oxadiazolone may. This fact may have some bearing on the intracellular habit of *Mycobacterium leprae*. The oxadiazolone is, too, a good deal more stable chemically than isoniazid. For example, it resists hydrolysis much better than the hydrazide. Thus, isoniazid and pyridyl-oxadiazolone may indeed possess similar biological properties, but their chemical and physical properties are widely divergent, which facts may influence their transport at a cellular level.

3. Some leprologists are of the opinion that isoniazid does possess an

TABLE I

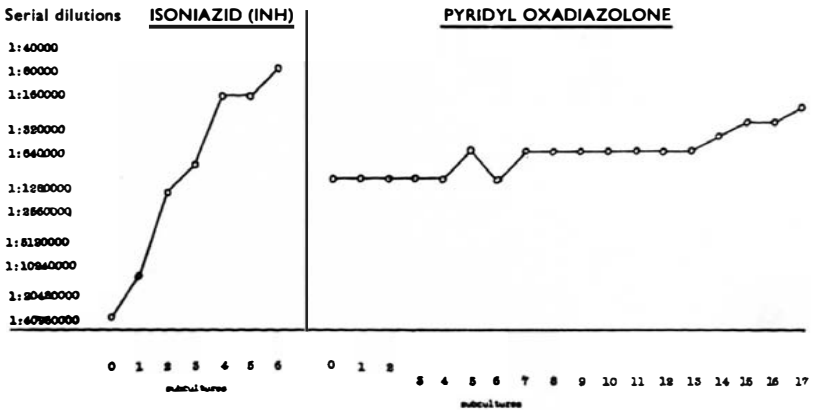


TABLE II

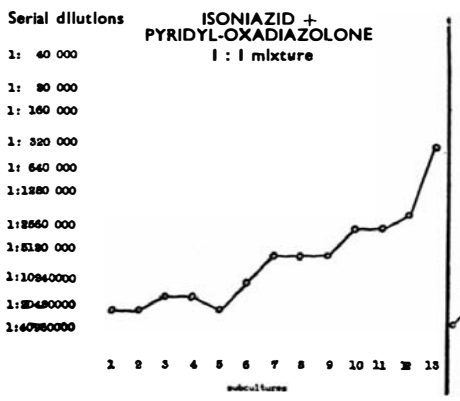


TABLE III

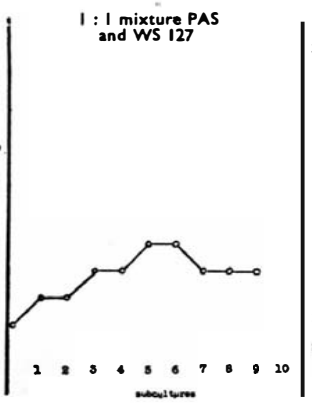
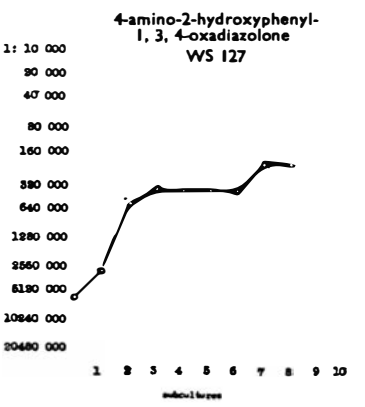


TABLE IV

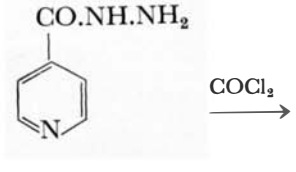


ephemeral action against *Mycobacterium leprae*, but that after 3–10 weeks resistance supervenes. The lower rate of resistance emergence against H37 Rv in the case of pyridyl-oxadiazolone might thus be reflected in its leprostatic activity in the clinic. The purely biochemical explanation of the above may be that the pyridyl-oxadiazolone and its analogues block the enzyme system responsible for the metabolic degradation of isoniazid or other tuberculostatic. In the course of the past three years we have had occasion to extend our observations to other oxadiazolones: p-amino-o-hydroxy-phenyl-1, 3, 4-oxadiazolone (WS 127) shows, as already pointed out, about the same tuberculostatic activity as p-amino-salicylic acid and 80–90 per cent cross resistance with it. The oxadiazolone is much more slowly eliminated by the human than PAS. Although PAS shows very little leprostatic activity, WS 127 shows, in the few cases of leprosy so far treated with it, a slight but definite leprostatic action.[7] In tuberculosis WS 127 is a suitable non-toxic, chemically stable and active substitute for PAS, for use in association with isoniazid.

Isoniazid may be converted to 4-pyridyl-1, 3, 4-oxadiazol-thione-5 (WS 202), by reaction with thiophosgene.[8] Here again WS 202 is definitely leprostatic,[9] though less so than its oxygenated analogue.

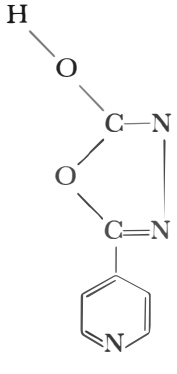
It would thus seem possible in the few cases so far studied to introduce leprostatic properties to tuberculostatics of the hydrazide class, which are normally devoid of tuberculostatic action, by cyclising the hydrazide group to the corresponding oxadiazolone or oxadiazol-thione.[10]

These relationships are shown in the following schemes:



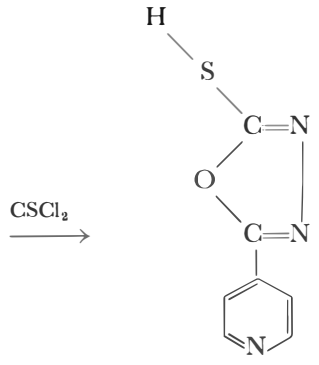
isoniazid

(+++) tuberculostasis
(−) leprostasis



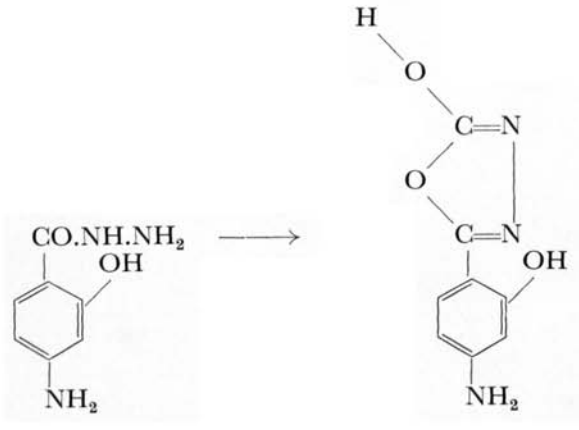
(++) tuberculostasis
(++) leprostasis

4-Pyridyl-oxadiazolone-(5)
(Vadrine≡p-amino-salicylate).



(++) tuberculostasis
(+) leprostasis

4-Pyridyl-oxadiazol-thione-(5)
(WS 202)



p-Amino-salicylic acid hydrazide

(++) tuberculostasis
(−) leprostasis

p-Amino-o-hydroxy-phenyl-1,3,4-oxadiazolone-(5)
(WS 127)

(++) tuberculostasis
(+) leprostasis

Further research is in progress on the above lines.

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Mycobacterium Leprae: A House Divided?

M. G. CORCOS, M.R.C.S., L.R.C.P., D.T.M. AND H.

*'And if a house be divided against itself, that house cannot stand.'**

The relationship between the tuberculoid granuloma and the lepromatous infiltrate has always been something of a puzzle. The former appears to be destroying lepra bacilli, whereas the latter seems to be aiding, perhaps even causing their reproduction.

When both these types of response are occurring in the same skin area of a patient, at the same time, what are we to think?

If the foregoing facts are acceptable as a result of the accumulation of evidence gathered over the years, re-examination of ideas about the relationship of the lepra bacillus to human host tissues seems justifiable.

The following two cases are cited, not because they are in any way unusual, but because the findings do seem to point to the extreme probability of tuberculoid and lepromatous responses being functionally opposite in their activity on the bacillus.

CASE 1 The patient was an Ibo man aged about twenty-seven, who had first noticed signs on his body a few months prior to coming under observation, and had had no treatment of any kind. On examination, his skin showed a few scattered slightly hypopigmented flat macules with rather poorly defined edges. (Fig. 1.) In addition to the frank macules, there were faintly hypopigmented areas on the front of the chest, face, arms and legs. With the exception of Macule M., none of the macules showed any anaesthesia, nor central repigmentation. Both ulnar nerves were considerably enlarged, but there was no anaethesia in the peripheral distribution of these nerves when the patient was first seen.

In making skin smears, the slit method of Wade (1935) was employed, the numbers of bacilli seen being indicated by the notation of Dharmendra (1952).

Mitsuda lepromin was used, the early and late results being read. (In this case, the size of the papules was not measured, but the positive readings were only weakly so.) Except where otherwise indicated, all investigations were made before treatment was started. The results are shown in detail in Fig. 2.

The histology at the edge of Macule M., showed tuberculoid and lepromatous features in the same section, both of minor intensity. A few acid-fast bacilli were seen in these sections. The centre of the macule showed resolution, with no acid-fast bacilli, and no recognisable nerve tissue.

*St. Mark, Ch. 3, vs. 25.

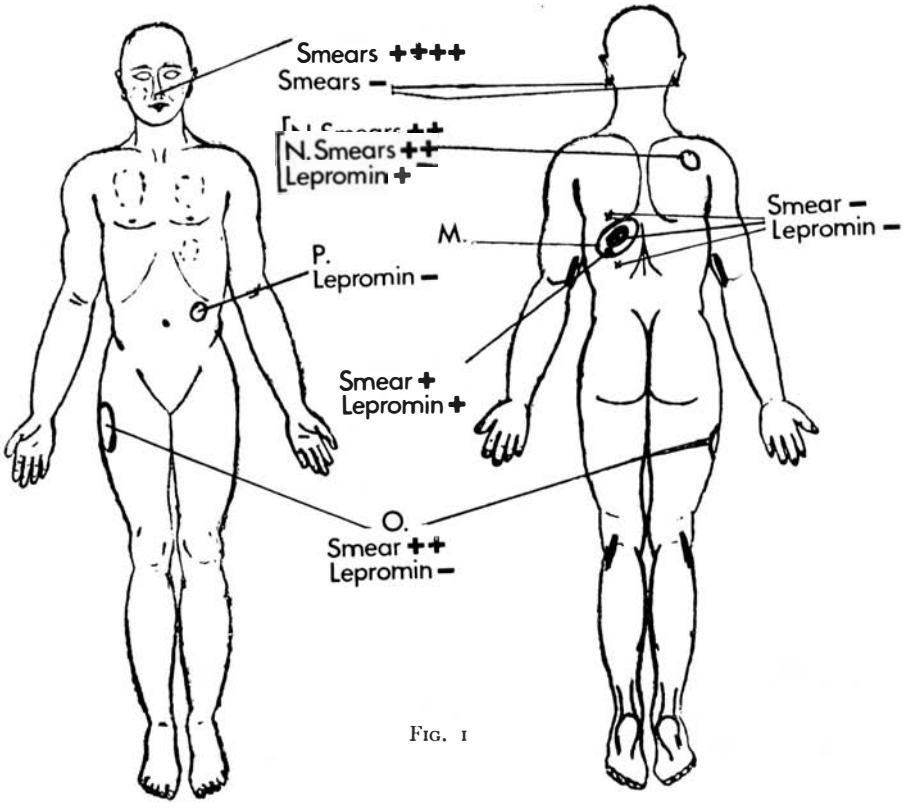


FIG. 1

On treatment with Dapsone, the subsequent progress of this patient was excellent. Two years after he had first been seen, all macules had completely disappeared. There was some persistent loss of tactile sensation in the area where macule M. had been. There was slight thickening of the right ulnar and right external popliteal nerves, with loss of tactile sensation along the right little finger and the dorsum of the left foot. Otherwise he was fit.

CASE 2 This was a Sierra Leonean man aged about forty-eight. Early in 1949, he had noticed a number of very faint ill-defined patches on his skin for which he was referred for specialist opinion. Skin scrapings and nasal smears were taken, and were repeatedly negative, and at the time, it was evidently not considered that he was suffering from leprosy. A routine medical examination for administrative purposes in 1952 had shown no obvious clinical abnormality.

He was first seen by me in October 1957 complaining of pain and weakness of both hands and widespread skin lesions, both present since July of that year. On examination, he was found to have extensive raised infiltrated plaques over most of this body. He did not appear to be in lepra reaction, and the temperature was normal. The infiltrated areas showed no loss of pigment (see photograph) and were distributed as in

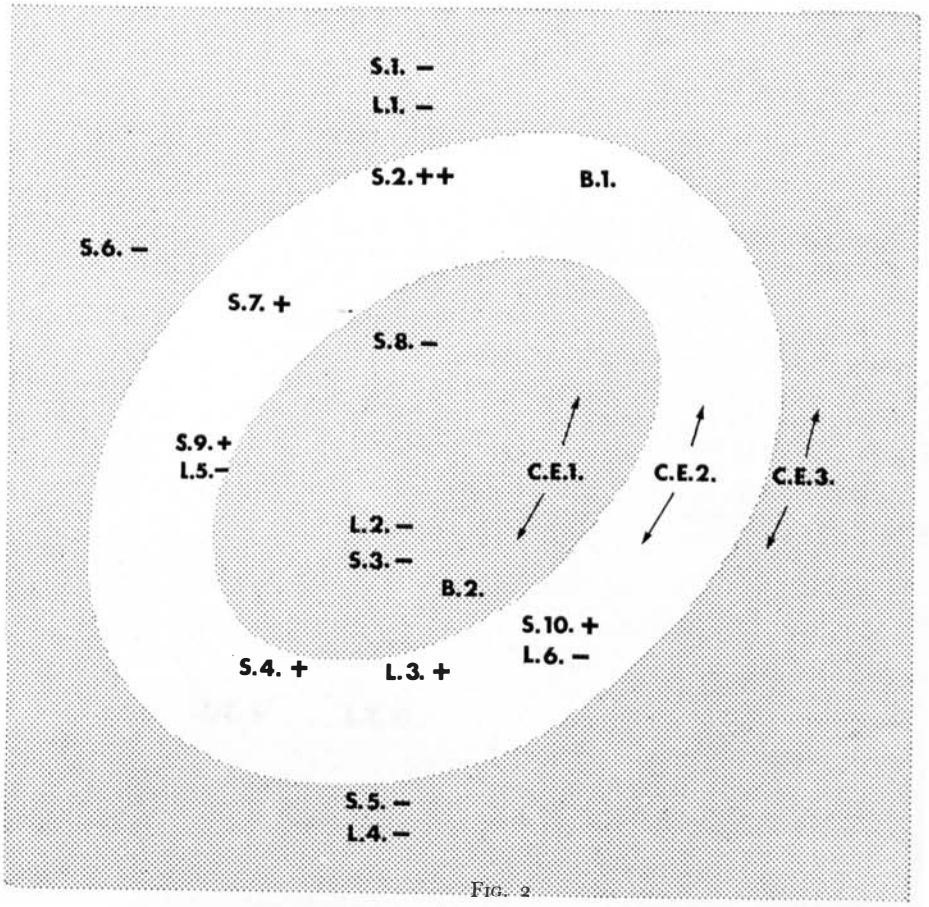


FIG. 2

S.1 Skin smear for bacilli taken 1st May.....—
S.2 Skin smear for bacilli taken 29th April.....++
S.3 Skin smear for bacilli taken 1st May.....—
S.4 Skin smear for bacilli taken 1st May.....+
S.5 Skin smear for bacilli taken 1st May.....—
S.6 Skin smear for bacilli taken 10th May.....—
S.7 Skin smear for bacilli taken 10th May.....+
S.8 Skin smear for bacilli taken 10th May.....—
S.9 Skin smear for bacilli taken 29th May.....+ (after starting treatment)
S.10 Skin smear for bacilli taken 29th May.....+ (after starting treatment)
L.1 Lepromin injected 1st May.....—
L.2 Lepromin injected 1st May.....—
L.3 Lepromin injected 1st May.....+
L.4 Lepromin injected 1st May.....—
L.5 Lepromin injected 29th May.....— (after starting treatment)
L.6 Lepromin injected 29th May.....— (after starting treatment)
B.1 Biopsy from hypopigmented skin taken 6th May.....See text
B.2 Biopsy from pigmented skin taken 6th May.....See text
C.E.1 Clinical examination done on the 1st May showed tactile and thermal anaesthesia of the pigmented skin at the centre of the patch.
C E.2 thermal anaesthesia only, of the hypopigmented skin at the periphery.
C.E.3 and no anaesthesia of the normally pigmented skin outside the patch.

Fig. 3. The patient was able to indicate with some certainty the sites of the original patches. Those over the back of the neck and over the right lower ribs were now concealed by the infiltration, and only an anaesthetic area was present on the back of the right thigh. On the front of the left thigh, however, infiltration was absent over an area of faintly hypopigmented anaesthetic skin, the site of an original patch.

There was marked tactile anaesthesia of both hands and feet, and patchy thermal anaesthesia of some infiltrated areas, especially around the sites of the old patches and on the face. The anaesthesia seemed to bear little relationship to the infiltrated areas, though generally speaking, the markedly infiltrated plaques tended not to be anaesthetic. An area of normal looking skin on which the patient was insistent there had been no previous patch, was anaesthetic to light touch. This area was on the front of the chest just to the right of the midline, in the distribution of the right medial supraclavicular nerve, which was not palpable.

There was bilateral VIIth nerve weakness, weakness of grip of both hands especially the left, and some paralysis of the interossei of both hands with slight wasting, particularly of the first right dorsal interosseous

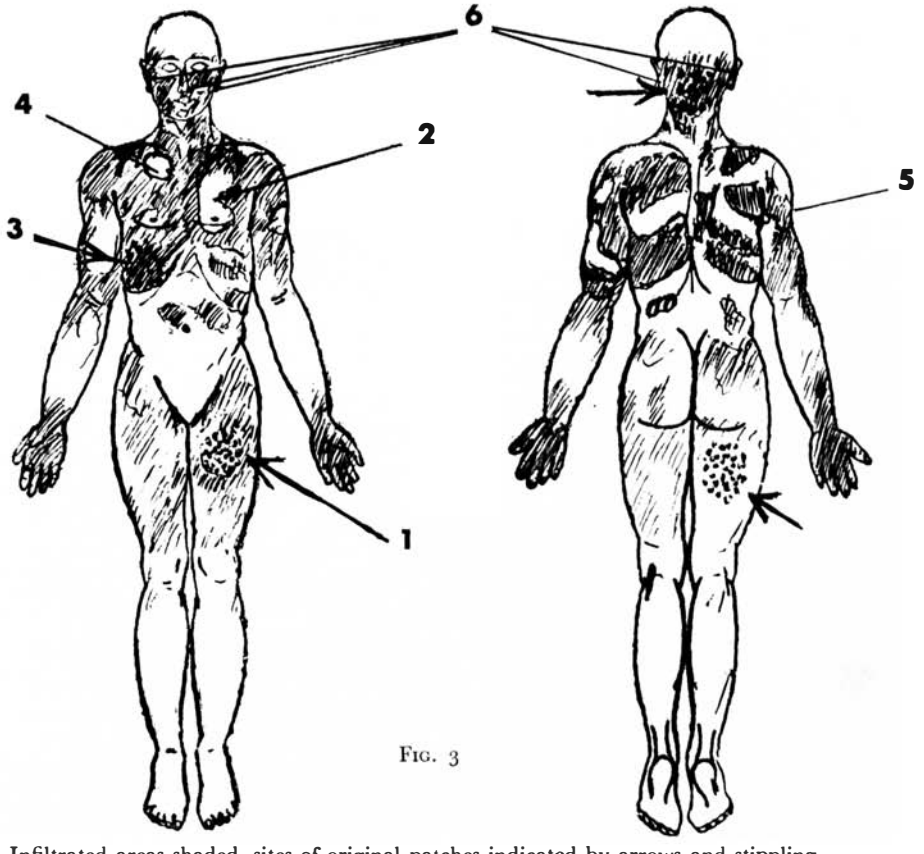


FIG. 3

Infiltrated areas shaded, sites of original patches indicated by arrows and stippling. Numbered sites – see Table I.

TABLE 1

SKIN SITE (SEE FIG. 3) CLINICAL	BACTERIOLOGY	IMMUNOLOGY		HISTOPATHOLOGY
4 Oct. 1957	4 Oct. 1957	19 Oct.	26 Oct.	4 Oct. 1957
1. Site of old patch on front of left thigh. Hypopigmented, anaesthetic, not infiltrated.	—ve	4 mm.	1 mm.	**1.** Centre of patch. Healed lesion.
2. Left chest, believed previously unaffected. Not anaesthetic.	Normal skin —ve	4 mm.	—ve	**2.** Edge of infiltrated area, including normal skin. Dimorphous lesion Lepromatous > Tuberculoid.
	Lesion +ve scanty	—ve.	—ve.	
3. Right lower ribs anteriorly. Infiltrated area over site of old patch which is no longer visible. Tactile anaesthesia absent, thermal anaesthesia present.	Normal skin —ve	2 mm.	1 mm	**3.** Edge of infiltrated area including normal skin. Dimorphous lesion Lepromatous > Tuberculoid. **3.** A. April 1958. Healed.
	Lesion +ve v. scanty	—ve	—ve	
4. Right upper chest believed previously unaffected. A patch of apparently normal skin, completely surrounded by raised non-anaesthetic infiltration.	Normal skin —ve	—ve	—ve	
	Lesion +ve scanty	—ve	—ve	
5. Right upper arm, believed previously unaffected. Not unaesthetic.	Lesion +ve v. scanty	—ve	—ve	
6. Right ear Left ear Nose (18 Dec. 1957)	+ve —ve +ve scanty			

REMARKS

Despite the rarity of the bacilli in some skin smears, and their extreme rarity in others, those that were found, showed normal staining and morphology.

muscle. There was rather marked right foot drop present, according to the patient since 1954. The right external popliteal nerve was palpable but not enlarged. The left external popliteal was very slightly enlarged. Other superficial nerves were clinically normal.

The lack of enlargement of the ulnar nerves was in striking contrast to the intensity of impairment of their function. Areas of thermal anaesthesia surrounded the fully anaesthetic areas on the back of the right thigh and on the front of the left thigh. No anaesthesia was found in the area of distribution of the enlarged supraclavicular nerves.

Investigations carried out before treatment was started, are shown in Table 1. Mitsuda lepromin was again used. Where the readings were positive, the diameter of the papule is shown in millimetres. All the early reactions were negative. The results in the Table are second and third week readings.

On the 29th October 1957, Dapsone therapy was started. The lesions underwent clinical change, becoming flatter, more hypopigmented and having slightly more sharply defined edges. On the 25th April 1958, a further biopsy was taken from the skin over the right lower ribs close to site 3 (= 3 A).

On the 17th May 1958, a further series of lepromin tests at previously tested sites, was made. The results were as follows:

	1st week	2nd week	3rd week
2. Left upper chest. Normal skin.	—ve.	—ve.	—ve.
Left upper chest. Infiltrated skin.	—ve.	—ve.	2 mm.
3. Right lower ribs. Normal skin.	—ve.	3 mm.	3 mm.
Right lower ribs. Infiltrated skin.	+ve.	3 mm.	3 mm.
4. Right upper chest. Normal skin.	—ve.	—ve.	—ve.
Right upper chest. Infiltrated skin.	—ve.	2 mm.	—ve.
5. Right upper arm. Infiltrated skin.	—ve.	2 mm.	—ve.

Skin smears from the above sites (avoiding the previous lepromin tests) taken on the 7th June 1958, were all negative.

DISCUSSION

A point of interest in these two patients is the relationship of the lepromin results to the lesions. A positive lepromin reaction was found on macule M., in an area clinically similar to one showing lepra bacilli and some degree of lepromatous histology. Other areas of this macule showed negative lepromin reactions despite the fact that the part biopsied was also considered to show tuberculoid histology. Macule N. showing positive skin smears was also lepromin positive at the site tested. Skin sites 2 and 3 in Case 2 were lepromin negative despite the fact that they showed some

epithelioid and giant cell histology. Lepromin negativity of a skin area already showing epithelioid and giant cells may well be analogous to the failure of lymphocytes in active cases of tuberculosis to exhibit a mitogenic effect in response to tuberculin, as found by PEARMAIN, LYCETTE and FITZGERALD (1963). It is probably an exhaustion phenomenon, in this case of an initially poor immune response.

Positive lepromin reactions in areas showing a tendency to lepra cell infiltration indicate that the ability of an area to produce a lepromatous response is not directly dependent upon its inability to produce a tuberculoid one. This is further borne out by the mixed histology referred to by KHANOLKAR (1959) and is exemplified by the sections of sites 2 and 3 in Case 2.

If, as seems likely on histological grounds (SCHUJMAN 1936, FERNÁNDEZ 1954), the tuberculoid granuloma is in fact an immune response to bacillary cytoplasm, destroying it, what of the lepromatous response? According to PEARMAIN, LYCETTE and FITZGERALD (1963), . . . 'The ability of immunologically competent cells to respond to antigen by mitosis appears to be a general character of the immune response'. It is therefore worth considering whether the lepromatous response may not also be an immune one directed against another bacillary antigen having quite different properties and behaviour from those of bacillary cytoplasm. Two such cellular responses to two bacillary antigens would accord with the findings of Nossal and Lederberg (1958) who showed that when an animal is stimulated with two contrasting antigens, individual cells tend to form one species of antibody.

A tuberculoid response to bacillary cytoplasm involving destruction of the latter, is not hard to envisage, but the lepromatous response is in an altogether different category. A number of workers, including DE SOUZA and DE SOUZA LIMA (1952), and CONVIT, LAPENTA, ILUKEVITCH and IMAEDA (1962), point to the seeming absolute dependence of the lepra bacillus on the lepra cell in order to live and multiply. If therefore the lepra cell is active against a bacillary antigen, this would have to be one tending to cause bacillary reproductive failure, and degradation of bacillary cytoplasm, since bacilli appear to remain morphologically intact and fully capable of reproduction when inside lepra cells (and probably Schwann cells), but fail to reproduce, and degenerate when they become extracellular, or when their host cell regresses.

In contrast to what seems to be the mechanism of the tuberculoid response, we cannot suppose that the lepra cell is destroying an antigen with the above mentioned properties, otherwise we should expect a lepra cell to produce bacilli that were subsequently able to live and multiply extracellularly.

It would be more reasonable to assume that an intra-bacillary factor is being rendered latent and sufficiently innocuous to the bacillus to allow the latter to reproduce. If the resultant bacilli each contained the factor, it would clearly be increasing in amount, in step with bacillary cytoplasm.

It might well be asked why a lepra cell should behave in the way here suggested. Perhaps it is a question of two antigens sharing the same bacillus but having different target organs. Thus if skin were the target organ of bacillary cytoplasm, whereas nerve tissue were the target organ of a bacillary antigen tending to destroy bacillary cytoplasm and inhibit bacillary reproduction, extreme variation in the pathological picture would result, depending upon the relative sensitivities of the target organs and upon the efficiencies of their immunologically competent protecting cells.

It is unlikely that morphologically intact bacilli are damaging the nerves of lepromatous patients, but quite possible that spontaneously degenerating ones are responsible for this type of damage, both in the later stages of lepromatous leprosy and in tuberculoid lesions.

Thus in Case 1, on Macule M, the anaesthesia was maximal at the site of resolution where skin smears were negative, but less at the site of activity where skin smears were positive. ROGERS and MUIR (1946) showed a section of a nerve branch in lepromatous leprosy with clumps of bacilli lying between undamaged nerve fibres. WEDDELL and PALMER (1963) have drawn attention to the findings of a fasciculus in a nerve bundle of a patient showing a tuberculoid lesion, undergoing degenerative changes in association with acid-fast 'dust', whereas an intact portion of the nerve bundle of the same patient showed two viable organisms lying in healthy Schwann cells related to healthy nerve fibres.

Supposing for the sake of argument, we term bacillary cytoplasm 'bacillary antigen', and the antigen against which lepra and possibly Schwann cells are assumed to be active 'anti-neural antigen', then the kind of dynamic relationships to be expected are shown diagrammatically in Fig. 4.

The behaviour of 'anti-neural antigen' as here envisaged, is suggestive of the presence in each bacillus of a biological self-replicating particle, possibly of a phage or virus-like nature. It is known that phages as well as having the lytic properties easily seen under laboratory conditions, may exhibit latency, and may also alter properties such as virulence and flagella production in their bacterial hosts (STOKER 1957). As long ago as 1939, CRUIKSHANK put forward the idea of the breakdown of a bacillus-phage complex having pathogenic effects in man, and it is known that the DNA of some phages is antigenic (BURNET 1963). In nature of course, it may be extremely difficult to distinguish between effects brought about by a phage, and those caused by a bacterial gene.

It will be appreciated that in a concept of the kind under discussion, the macrophage that will later become a lepra cell, must be something more than a scavenger. If it is to be regarded as inhibiting a neuropathogenic factor in a lepra bacillus which reproduces as a consequence, some degree of negative neurotropism would be expected of it. It may be that the 'ideal' lepra cell after engulfing a degenerating bacillus threatening a nerve fibril, moves away from the nerve to a safe distance before

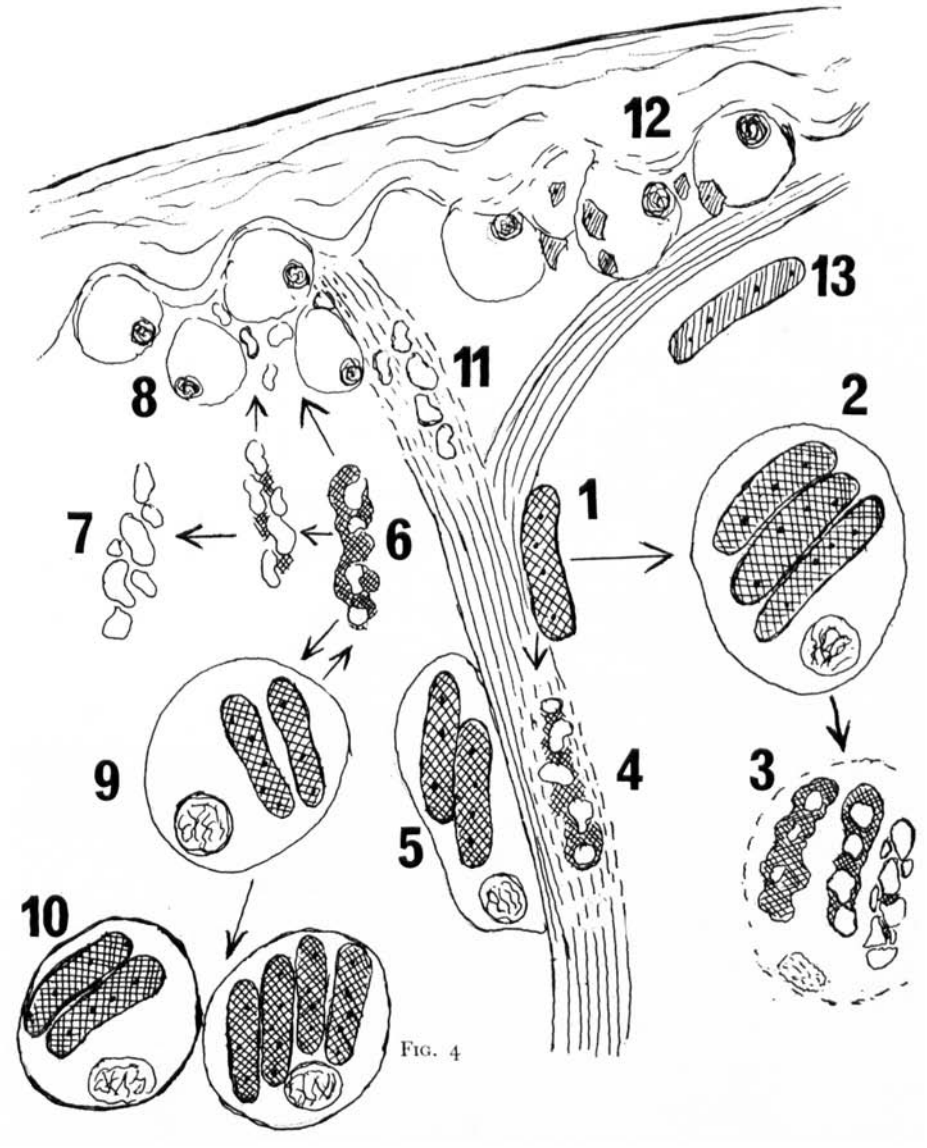


FIG. 4

LEGEND TO FIGURE 4

= Live 'bacillary antigen' (= bacillary cytoplasm). Harms skin.

= Latent 'anti-neural antigen', alive or dead. Harmless to nerve.

= Active 'anti-neural antigen'. Harms nerve.

= Killed 'bacillary antigen' (= lepromin).

The arrows indicate stages in pathogenesis, *not* movement.

1. Live extracellular bacillus adjacent to nerve. 'Anti-neural antigen' still latent. No nerve damage.

2. Bacillus engulfed by lepra cell. 'Anti-neural antigen' kept in latent state, therefore bacillus reproduces and 'anti-neural antigen' increases.

3. Lepra cell degenerates, therefore 'anti-neural antigen' becomes active, and in each bacillus increases *at expense of* 'bacillary antigen'.

4. Antigens behaving as in **3** above, but in nerve fibre which is damaged by 'anti-neural antigen'.

5. Schwann cell behaving like lepra cell, protecting nerve by keeping 'anti-neural antigen' latent, and therefore bacilli morphologically intact.

6. Live 'anti-neural antigen' destroying live 'bacillary antigen' when both are at a distance from nerve.

7. The process completed, no 'bacillary antigen' remains, and there is no tissue damage.

8. Lepra cells protect bacilli from epithelioid cells, which can only affect extracellular forms. The decreasing 'bacillary antigen' is destroyed, but the increasing 'anti-neural antigen' is ignored by epithelioid cells and remains free to inflict nerve damage.

9. Degenerating lepra bacillus is engulfed by lepra cell, 'anti-neural antigen' is rendered latent, bacillus regenerates and reproduces in cell.

10. When functional efficiency of lepra cell begins to decline, increased amounts of latent 'anti-neural antigen' begin to become active (see **3**). This activity is mitogenic to the lepra cell, which divides. The two daughter cells again become efficient in maintaining 'anti-neural antigen' in the latent state, and bacillary reproduction is maintained.

11. Nerve in tuberculoid part of lesion damaged by 'anti-neural antigen'.

12. Positive lepromin reaction. Heat stable whole killed bacilli broken down and destroyed by epithelioid cells.

13. Negative lepromin reaction. Killed 'bacillary antigen' tolerated by tissues of lepromatous patient or area. 'Anti-neural antigen' killed while in latent state has lost potential antigenicity and pathogenicity.

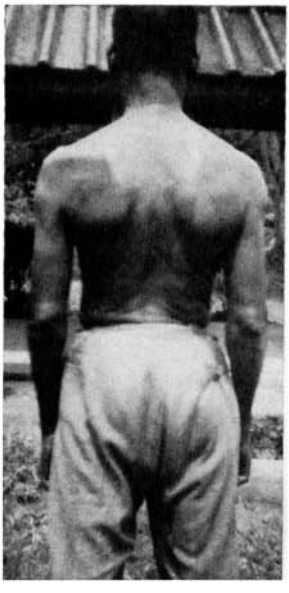
shedding the resultant increased bacillary load into the connective tissue and reverting to its undifferentiated state.

The bacilli degenerate harmlessly, and the human host does not get leprosy. Trouble might well start where a lepra bacillus is taken up by a relatively non-motile cell having a high potentially for (indirectly) inducing bacillary reproduction, and for division in order to 'keep pace' with its increasing bacillary load.

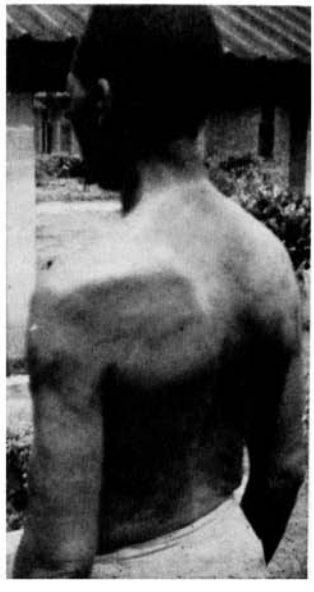
It is felt that the clinico-pathological picture in the two cases here presented is explicable on the basis of skin and nerve sensitivities to two bacillary antigens related to each other in the manner described. Other forms of leprosy and of freedom from it may be similarly explained. Thus pure lepromatous leprosy results from the infection of a person whose nerves are sensitive to 'anti-neural antigen' but whose skin is tolerant of

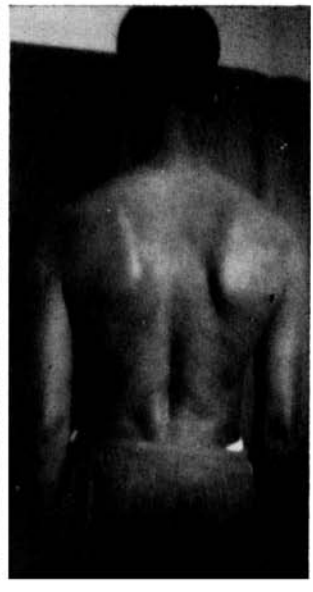
'bacillary antigen'. Tuberculoid and mixed lesions are produced where nerves are sensitive to 'anti-neural antigen' and skin is sensitive to bacillary antigen, the precise clinical type depending upon the relative magnitudes of the two sensitivities and upon the efficiencies of the two kinds of immunologically competent protecting cells in relation to them. A person whose skin is sensitive to 'bacillary antigen' but whose nerves are tolerant of 'anti-neural' antigen would be lepromin positive but incapable of acquiring leprosy, since there would be no stimulus to the production of lepra cells in his tissues, hence no bacillary multiplication. Similarly, a person whose skin is tolerant of 'bacillary antigen' and whose nerves are also tolerant of 'anti-neural antigen', would be lepromin negative, but equally incapable of acquiring leprosy. The same considerations could well apply to skin areas rather than persons.

'Anti-neural antigen', if it exists might well be difficult to demonstrate, especially if it is heat labile. It may be thought of in its active form as occupying the same space as bacillary cytoplasm but as having an inverse time relationship with it, and the temptation is strong to identify it with the non-stainable electron transparent material that seems to displace cytoplasm in extracellular forms. It could be that in looking at a 'granular form' we are witnessing not so much the death of a bacillus as a stage in the transformation of a lowly form of life into a yet lower one. The concept of the spontaneous change of one living antigen into another only prevented by the increase of both may give a clue to the mechanisms involved in lepra reaction, but this paper is too short to explore these further possibilities.



CASE 2. When first seen.





CASE 2. Seven months after the start of treatment.

REPORT ON BIOPSY SPECIMENS FROM CASE 2
(See Table 1)

SITE NO. 1

H. E. Section There is a round cell and histiocytic infiltration underneath the epidermis of slight intensity with some evidences of a narrow but free subepidermal zone. In the corium proper there seems to be a considerable increase in collagen and very few recognisable skin appendages. There is one area where there is a small focus of epithelioid cells. In one or two areas of slight infiltration there appears to be nerve tissue. This is rather difficult to be certain of, otherwise, there is nothing very characteristic about this section, and one would consider that there is considerable evidence of fibrosis or scarring.

F. F. Stain No acid fast bacilli seen.

Diagnosis This is consistent with a lesion which is healed. It is not possible to type or group the case. The only indication is the residual focus of epithelioid cells, but this is not characteristic enough to give an opinion on the section.

SITE NO. 2

H. E. Section There is a broad band of infiltration below the epidermis leaving a clear subepidermal zone. The infiltrate consists of round cells and histiocytes some of which have the appearance of epithelioid cells and there is an occasional giant cell. It is difficult to say whether there is any foamy cell change or not. This is a section fixed by the Ridley's technique, and there may have been a little distortion of the cellular elements. In the dermis proper a similar infiltrate is seen around the appendages of the skin and there are one or two quite definite epithelioid foci with again, an occasional giant cell. One nerve shows interesting infiltration, the epineurium is proliferated, and there are epithelioid cells in the centre of the nerve.

F. F. Stain No acid fast bacilli seen. The nerves in this section are more easily recognised and there seems to be some increase in Schwann cells.

Diagnosis This is a dimorphous lesion considerably nearer to the lepromatous end of the spectrum rather than the tuberculoid, but the fact that there are no acid fast bacilli seen in Fite section makes it difficult to say more than this.

SITE NO. 3

H. E. Section Again there is a broad band of granulomatous infiltration underneath the epidermis leaving a clear subepidermal zone. The infiltrating cells consist of macrophages, round cells and some of the macrophages are definitely epithelioid cells, there appears also to be some foamy cell change. In the deeper parts of the dermis there is the appearance of increased collagen, round the appendages of the skin there is a similar infiltrate. Here there are one or two giant cells and one or two definite epithelioid foci. Nerves by and large are uninvaded although there is an increase in the cellular element and a proliferation of the epineurium.

F. F. Stain Again, unfortunately, no acid fast bacilli are seen.

Diagnosis This appears to be a dimorphous lesion, nearer to the lepromatous end of the spectrum than the tuberculoid. The absence of acid fast bacilli suggests that there is still a considerable tuberculoid element in the section.

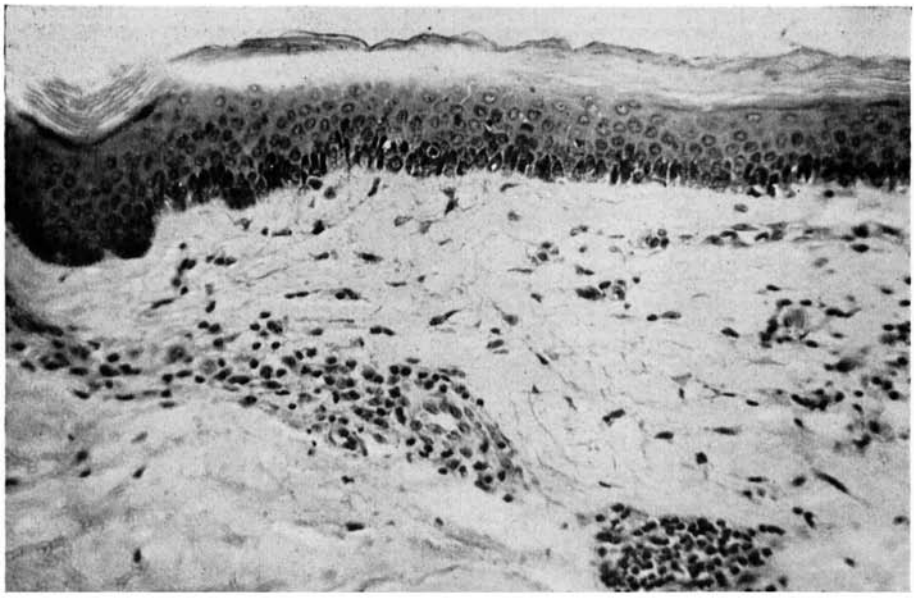
SITE NO. 3A

Taken on 25 April 1958 from close to site No. 3. At this time the patient was undergoing oral Dapsone treatment.

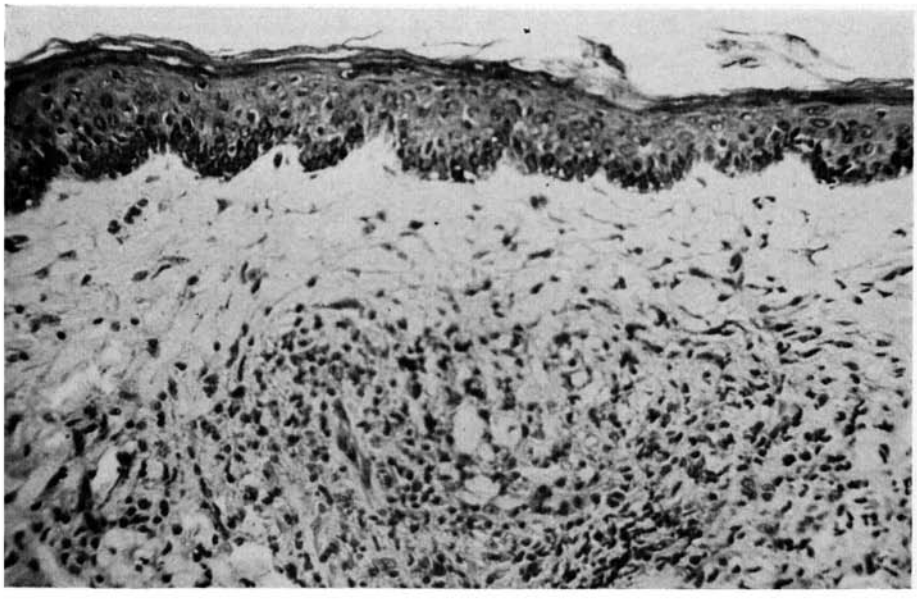
H. E. Section Scattered round-celled and histiocytic infiltration immediately underneath the epidermis of moderate intensity. In the deeper layers of the corium there is considerable increase of collagen fibres and there is very little evidence of skin appendages. There is also a slight round-celled infiltration. No nerves definitely seen.

F. F. Stain No acid-fast bacilli.

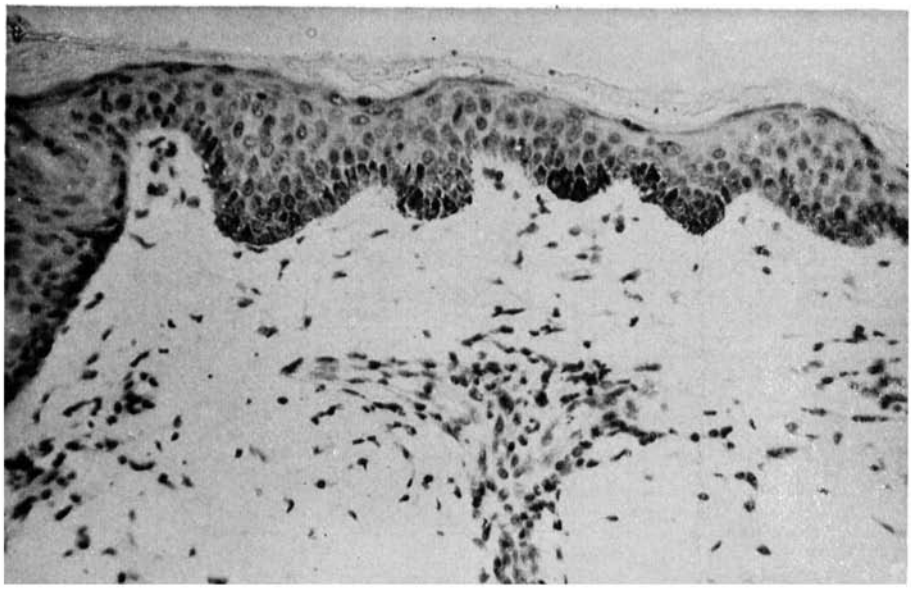
Diagnosis This is an indeterminate or undiagnostic histology, but would fit in with a healed or scarred lesion.



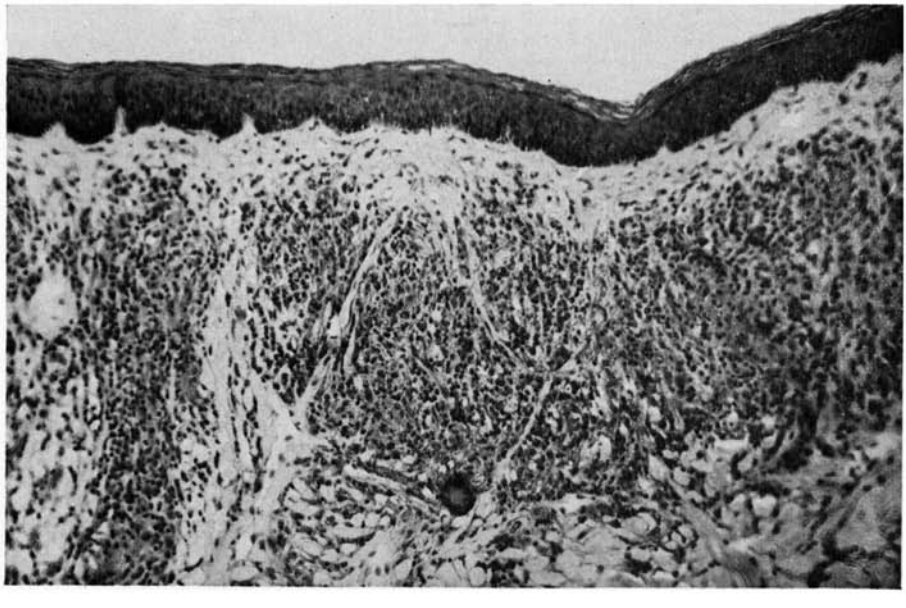
CASE 2. Section from site No. 1. Fite-Faraco stain. × 300.



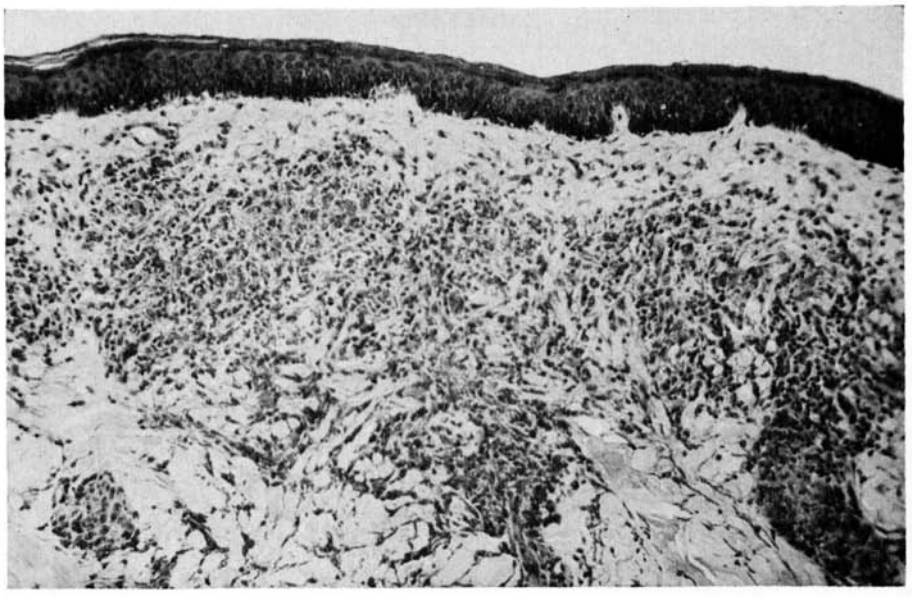
CASE 2. Section from site No. 2. Fite-Faraco stain. × 300.



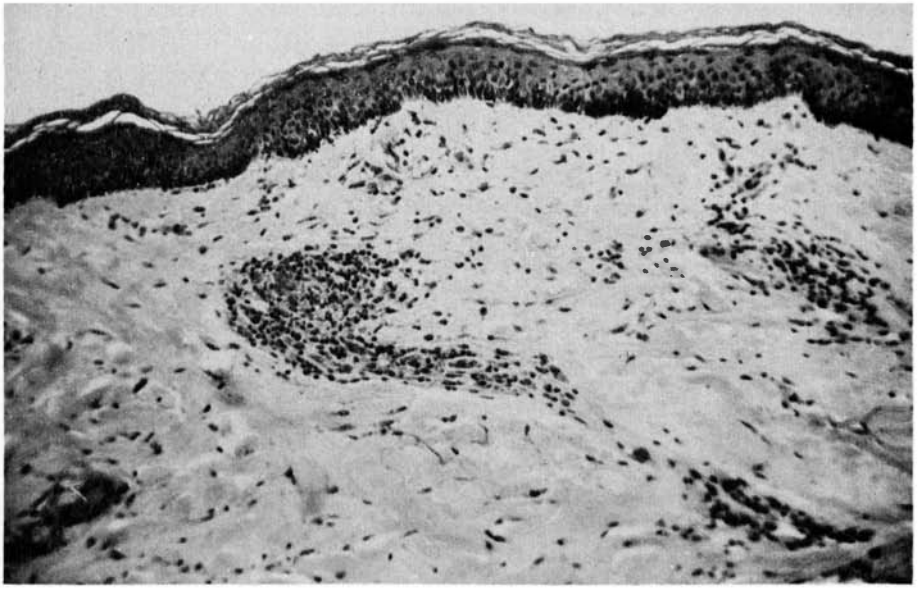
CASE 2. Section from site No. 2. Haematoxylin and eosin stain. × 300.



CASE 2. Section from site No. 3. Fite-Faraco stain. × 150.



CASE 2. Section from site No. 3. Fite-Faraco stain. × 150.



CASE 2. Section from site No. 3A. Fite-Faraco stain. × 150.

SUMMARY

Two cases of leprosy of mixed type are described. Bacilli were not found in the clinically normal skin of either case, whether it was lepromin positive or negative, but they were present in the lesions which showed features of the tuberculoid and lepromatous responses intermingled with each other.

The presence of a poorly developed lepromatous infiltrate did not appear to exclude a positive lepromin reaction in a clinically similar part of the lesion neither did the prior development of epithelioid and giant cells exclude lepromin negativity of the lesion very close to where they were found.

On the basis of these findings, the following is suggested:

There are two antigens in each leprosy bacillus. The one to which the tuberculoid granuloma is the response is bacillary cytoplasm. It is heat stable and has the skin of sensitive subjects as its main target organ. It is destroyed by epithelioid and giant cells, and also by another heat labile bacillary antigen which when active also causes damage to nerve in sensitive subjects. This second antigen is rendered latent by lepra and Schwann cells, and hence harmless both to nerves and bacilli. The latter are thereby enabled to reproduce. The second antigen may be a living self-replicating particle always carried by lepra bacilli.

ACKNOWLEDGEMENT

I am indebted to DR. T. F. DAVEY, DR. R. G. COCHRANE, DR. G. BERRY, MR. J. UWOM, MR. D. WHITE, MISS F. MCNULTEY and MISS A. BOYNES for their help in the collection and preparation of the material on which this paper is based. None of these workers necessarily endorses the views expressed in the discussion, for which I must bear the sole blame.

I would particularly like to thank the two patients for their willing and intelligent co-operation.

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Leprotic Involvement of Multiple Peripheral Nerves in the Absence of Skin Lesions

(A case report)

J. C. HARGRAVE, M.B.; B.S.; D.T.M. & H.
(Medical Officer in Charge, East Arm Leprosarium, Darwin)

and

REV. MOTHER MARION, O.B.E.; F.D.N.S.C.; S.R.N.
(Mother Superior, East Arm Leprosarium, Darwin)

In 1957 a four-year-old full-blood male aboriginal of the Gunuinggu Tribe from the Liverpool River in Central Arnhem Land, Northern Australia, was diagnosed as having leprosy. His only clinical signs were a considerably enlarged left ulnar nerve, associated with slight wasting of the small muscles of the left hand. Neither then nor later were any skin lesions apparent.

Treatment with diaminodiphenylsulphone was commenced on an outpatient basis. His parents, who belong to a primitive group of tribesmen, fearing the child might be isolated at the leprosarium took him away from the treatment centre and interrupted his treatment. In the vast, undeveloped tracts of Arnhem Land it is comparatively easy to escape surveillance and this child was not seen again for two years.

In 1959, when next seen, it was found that, in addition to the original signs, his left lateral popliteal nerve was enlarged and firm. A further attempt at outpatient treatment met with the same fate as the first. He was next seen in September, 1960. Although his signs were unchanged, he was admitted to the leprosarium to ensure continuity of treatment and observation.

As an inpatient at the leprosarium, despite regular treatment with diaminodiphenylsulphone, he remained a thin, under-developed child, weight gain was slow (7 pounds in 2½ years) and there was progressive involvement of the peripheral nerves.

By July 1961 both ulnar nerves and the left lateral popliteal nerve were grossly enlarged. In March 1962 the right lateral popliteal nerve was also moderately enlarged and both median nerves were readily palpable above the wrist.

In March 1963, another detailed examination was made for neural involvement. The results of this were thought to be unusual and interesting and are set out opposite.

NECK AND TRUNK

Both Great Auricular Nerves were palpable but normal.
The lateral branch of the right supraclavicular nerve was enlarged for a distance of 2 cm. over the lateral third of the clavicle.

UPPER LIMBS

Right

Ulnar Nerve
Grossly enlarged for 12 cm. above the elbow.

Median Nerve
Grossly enlarged for 7 cm. above the carpal tunnel and also 5 cm. above the elbow in the mid-arm.

Radial Nerve
Grossly enlarged for 5 cm. above the elbow.

Dorsal Branch of Ulnar Nerve
Enlarged and hard.

Terminal Branch of Radial Nerve
Grossly enlarged for 14 cm. above the wrist.

Lateral Antebrachial Cutaneous Nerve
Enlarged for 12 cm. below the elbow.

Medial Antebrachial Cutaneous Nerve
Enlarged for 5 cm. below the elbow.

Posterior Antebrachial Cutaneous Nerve
Enlarged, hard and nodular for 9 cm. below the elbow.

Left

Ulnar Nerve
Grossly enlarged for 12 cm. above the elbow but palpable up to the axilla.

Median Nerve
Grossly enlarged for 4 cm. above the carpal tunnel.

Radial Nerve
Grossly enlarged for 6 cm. above the elbow.

Dorsal Branch of Ulnar Nerve
Not palpable.

Terminal Branch of Radial Nerve
Enlarged for 6 cm. above the wrist.

Lateral Antebrachial Cutaneous Nerve
Enlarged for 12 cm. below the elbow.

Medial Antebrachial Cutaneous Nerve
Enlarged for 5 cm. below the elbow.

Posterior Antebrachial Cutaneous Nerve
Palpable before reaching the forearm from mid-arm to elbow.

LOWER LIMBS

Right

Lateral Popliteal Nerve
Grossly enlarged for 5 cm. about the neck of the fibula.

Posterial Tibial Nerve
Grossly enlarged behind the medial malleolus and greater in size than on the left.

Musculocutaneous Nerve
Grossly enlarged in the lower third of the leg to the level of the ankle joint.

Sural Nerve
Enlarged in the lower three-quarters of the calf.

Infrapatellar Nerve
Palpable for a distance of 5 cm.

Lateral Cutaneous Nerve of the Thigh
Palpably enlarged in the middle third of the thigh.

Medial Femoral Cutaneous Nerve
Not palpable.

Lateral Cutaneous Nerve of Calf
Palpable just medial to the lateral popliteal nerve behind the knee.

Left

Lateral Popliteal Nerve
Grossly enlarged for 4 cm. about the head and neck of the fibula.

Posterior Tibial Nerve
Enlarged behind the medial malleolus.

Musculocutaneous Nerve
Enlarged for same distance as the right but smaller in size.

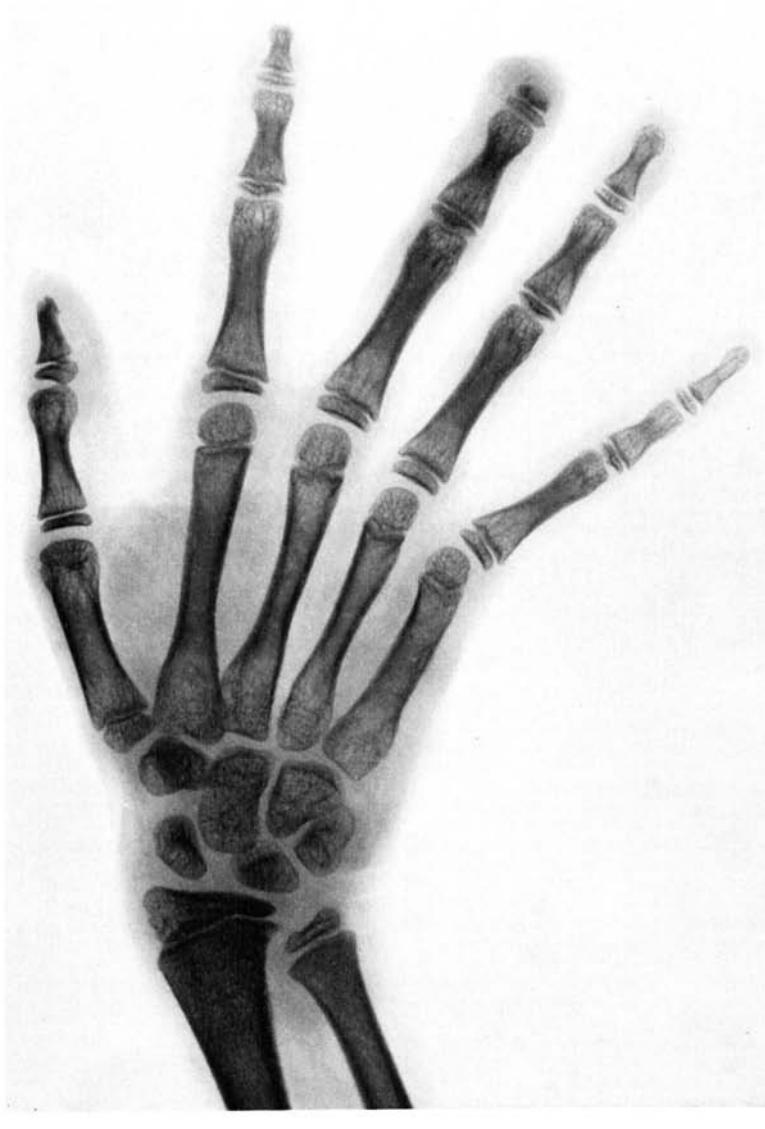
Sural Nerve
Grossly enlarged in the lower half of the calf.

Infrapatellar Nerve
Not palpable.

Lateral Cutaneous Nerve of the Thigh
Not palpable.

Medial Femoral Cutaneous Nerve
Palpably enlarged for a distance of 3 cm. at about 10 cm. above the knee.

Lateral Cutaneous Nerve of Calf
Not palpable.



X-ray of right hand showing early resorption of tips of thumb, index and middle fingers.

OTHER PHYSICAL FINDINGS

A very thin, ten-year-old aboriginal boy

The Histological report on a section of the terminal branch of the radial nerve was: 'There are collections of inflammatory cells within the nerve. These tend to be focally arranged and consist chiefly of lymphocyte-like cells with some macrophages. This appearance could occur in Leprosy.'

RIGHT UPPER LIMB

There were old scars on the tips of the thumb, index and middle fingers, with early resorption of the terminal phalanges. Wasting in the thenar eminence was obvious but was only slight in the hypothenar eminence.

The following muscles were found to be weakened in action: Flexor pollicis brevis, Abductor pollicis brevis and all the interossei. The Flexor digitorum profundus to the ring and little fingers was weak and the Flexor carpi ulnaris action was almost absent. There was no demonstrable weakness in the action of the lumbricals.

Sensation to pinprick was normal, but sensation to light touch, though present, was dimished and localisation was poor. The language barrier and the age of the patient made the testing of thermal sensation difficult. The thumb, index and middle fingers were dry but the ring and little fingers were moist to the touch.

LEFT UPPER LIMB

The left forearm was very thin and there were some small burn scars over the left olecranon. The thenar and hypothenar eminences were wasted and the 4th and 5th fingers were clawed.

The unassisted angles (Brand 1959) of the proximal interphalangeal joints were:
Index = 44°; Middle = 56°; Ring = 98°; Little = 98°.

The assisted angles were:
Index = 0°; Middle = 0°; Ring = 41°; Little = 56°.

Contractures in these joints were:
Ring = 24°; Little = 34°.

The following muscles were completely paralysed: All the Lumbricals, Flexor carpi ulnaris and Flexor digitorum profundus to the ring and little fingers, and the Adductor pollicis.

The abductor pollicies brevis and the Flexor pollicis brevis were weak.

The Opponens pollicis appeared to be normal in action after passively initiating and aiding abduction. The whole hand was dry and completely anaesthetic except over the lateral side of the volar aspect. Localisation was poor and the precise boundaries of anaesthesia almost impossible to define accurately.

LOWER LIMBS

There was no sensory defect or muscular paralysis in either leg. Sweating appeared to be normal.

Following this detailed examination (March 1963), a course of Prednisone at a dosage level of 5 mgm. t.d.s. was commenced in the hope of reducing the amount of fibrosis in the enlarged nerves. After six months the dose was reduced to 5 mgm. b.d. and has continued at that level.

In October 1963 another detailed examination of the enlarged peripheral nerves showed that all were smaller in size, except the left median nerve, the left lateral popliteal nerve and both posterior tibial nerves. These appeared to be unchanged.

Other physical findings at this latter date remained the same. Weight gain over the same period was five pounds.

DISCUSSION

Palpable enlargement of certain peripheral nerves in leprosy is extremely common (DHARMENDRA 1960 et al). What, in the author's opinion, is unusual is to encounter such a large number of palpably enlarged peripheral nerves simultaneously.

BRAND (1959) has pointed out that freedom of peripheral nerves from involvement depends on their depth from the surface and is, therefore, related to temperature. This patient, being a very thin child with a minimum of superficial fat, may on that account have been more prone to peripheral neural involvement.

The relationship of prednisone therapy to the diminishing size of the nerves is, at best, of dubious significance in an isolated case. It is mentioned only in view of possible subsequent value. It is a matter of common experience that one finds very small, hard nerves with a considerable degree of deformity in the late stages of leprosy. It is, then, quite possible that the diminishing size of these nerves indicates that they are undergoing this process and will, in time, produce this deformity. This will be interesting matter for future observation.

ACKNOWLEDGEMENTS

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Effect of Injection of Hydrocortisone into Nerves Thickened by Leprosy

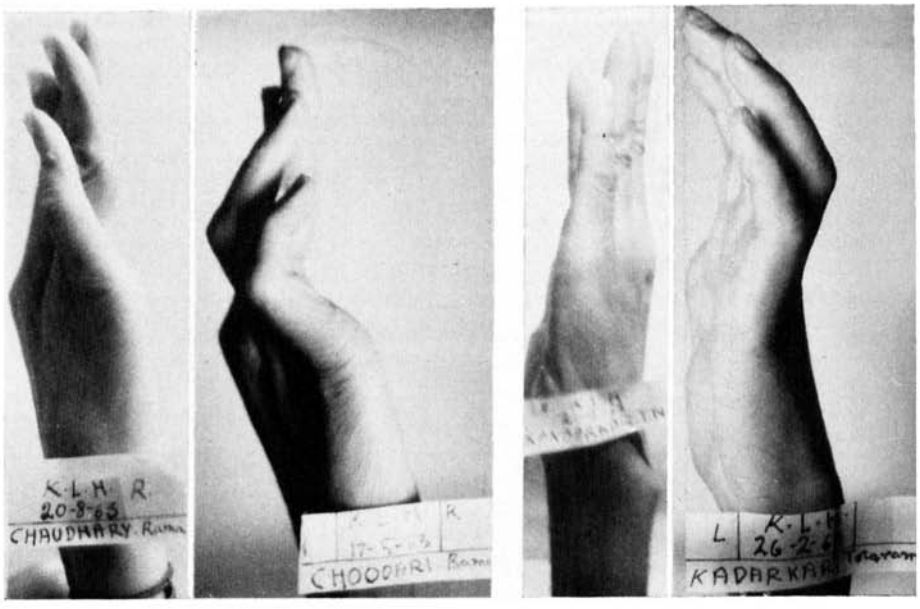
W. H. JENNINGS,
Physiotherapist, Kondhwa Leprosy Hospital, Poona, India
(*By courtesy of the Honorary Surgeons and Honorary Superintendent, Kondhwa Leprosy Hospital*).

Perineural infiltration of hydrocortisone was carried out on 12 patients with nerves thickened due to leprosy, at the Kondhwa Leprosy Hospital, and the drug was found very efficacious in the patients treated early. The patients treated were of all the three main types of leprosy.

TECHNIQUE

Hydrocortisone was injected round the lesioned nerve; 50 mg. twice a month (once in two weeks) in some cases, and in the other cases 25 mg. hydrocortisone diluted with 3 c.c. distilled water once a week. No hyaluronidase was used with hydrocortisone. Standard physiotherapy of electrical muscle stimulation, voluntary exercises of the involved muscles and splinting of the limb was administered to cases of complete paralysis.

Results: In the 12 cases of cortisone treatment observed, 3 among these cases, one a pure lepromatous and the other two pure tuberculoids, had lesions on the ulnar nerve of more than a year in duration with paralysis of the intrinsic muscles supplied by the ulnar nerve to the degree of complete reaction of denervation. They did not respond to hydrocortisone treatment, 50 mg. given twice at the interval between each injection mentioned above. The remaining nine cases benefited from the drug. Photographs indicate the recovery from ulnar palsy of two patients among the successful nine, MR. K. T. N. and MR. C. R. These two cases were of mixed leprosy. K.T.N. had severe neuromata of the ulnar nerve with anaesthesia in the region of the nerve supply and intrinsic muscle paralysis to the extent of partial reaction of denervation. He was first given hydrocortisone treatment 2 weeks after the signs of paralysis and anaesthesia, 25 mg. hydrocortisone diluted with 3 c.c. distilled water once a week. After the third injection signs of recovery from paralysis were noted. Hydrocortisone was discontinued but physiotherapy carried on. Two months after the first injection of cortisone he had totally recovered from paralysis and a partial recovery from anaesthesia was noted. A complete regression of the neuromata was noted within a month of starting treatment. R.C. had no neuromata but had an enlarged ulnar nerve. He was given treatment six months after the development of ulnar anaesthesia and intrinsic muscle paralysis, the degree of paralysis being partial reaction of denervation of the muscles. He had one injection of 50 mg. hydrocortisone round the affected area of the nerve and physiotherapy was begun, so that two weeks after the injection the nerve appeared normal on palpation, and six weeks after this almost total recovery from paralysis was



observed. There has not yet been sensory recovery in this case, though more than seven months have elapsed since the date of the injection.

Among the remaining seven cases, three patients of mixed leprosy and two of lepromatous leprosy had severe neuromata of the ulnar nerve, two among the mixed cases having very mild paralysis and anaesthesia. Each of these patients was put on cortisone treatment within two weeks of the appearance of signs of nerve involvement, by 50 mg. hydrocortisone given twice, round the site of the lesion. No physiotherapy of any nature was given to these five patients. Within two months of this treatment these five patients had normal nerves and the two had recovered from paralysis and anaesthesia. A tuberculoid case, among the remaining two, was given cortisone for bilateral foot drop, treatment being started within a month of the signs of lateral popliteal paralysis and the dosage being 25 mg. hydrocortisone injected round the affected area of each lateral popliteal nerve. Recovery was noted from paralysis within two weeks of the first injection and at this time he went home on leave for an emergency and did not return to complete his treatment. The last remaining case, of mixed leprosy, had a very enlarged and painful ulnar nerve with anaesthesia in the area of the nerve supply and partial atrophy of the hypothenar muscles. Cortisone and physiotherapy were begun a month after the signs of paralysis, dosage of the drug being 25 mg. hydrocortisone diluted with 3 c.c. distilled water once in a week. After four injections pain and swelling of the nerve subsided and though no recovery from paralysis or anaesthesia has been observed even after six months of the treatment there has also been no progress of the paralysis.

COMMENTS

In July 1959 there was an article in the *Leprosy Review* by W. H. JOPLING about the success of hydrocortisone treatment in a lepromatous case of foot-drop. This article is confirmatory of the facts mentioned by DR. JOPLING and any other persons who might have advocated the use of hydrocortisone in arresting or curing neural deformities due to leprosy.

SUMMARY

Hydrocortisone appears highly efficacious in preventing or curing neural deformities arising in connection with leprosy, the type of leprosy of the patient being immaterial provided treatment is started early.

THANKS:

In this work I was guided by DR. J. M. MEHTA, Honorary Plastic Surgeon, Kondhwa Leprosy Hospital, and I wish to thank him for his kind help which has made this article possible.

I also thank DR. N. J. BANDORAWALLA, Honorary Superintendent, Kondhwa Leprosy Hospital, for allowing me to publish this article.

Two Unusual Cases of Nerve Abscess

H. W. WHEATE,
Chazi Leprosarium, Tanganyika

Nerve abscess is a relatively rare complication of leprosy as has been reported by BROWNE (1957). The following two patients are of particular interest.

CASE I

A small boy aged 9 years referred by the doctor in charge of a local Mission hospital. The child had been under treatment with dapsone for a little under one year, having had a few mild tuberculoid patches. These had recently become much more obvious and a painful swelling over the right ulnar nerve had appeared, associated with clawing of the 4th and 5th fingers of the right hand.

On Examination: The clinical appearance of the skin lesions was of major tuberculoid leprosy in reaction. Smears were negative for *M. leprae.* There was a grossly enlarged cutaneous branch of the ulnar nerve on the dorsum of the right hand and a fusiform swelling, tender and hard with a fluctuant centre, of the main nerve trunk just above the epicondyle. Proximal and distal to this swelling the nerve was slightly thickened.

Treatment: It was considered that in a child of this age any major surgical intervention would be likely to do more damage to the nerve than had already been sustained. Accordingly, we merely incised the abscess (which contained fluid with the appearance and consistency of curds and whey) and inserted a small eusol wick.

It was decided that, in view of the history of recent reaction under dapsone therapy, this drug was contraindicated and that combined chemotherapy would be more effective than the use of any one drug. The combination selected was thiambutosine plus streptohydrazide. A short course of Prednisolone was also given. Simple daily massage of the right hand was prescribed to maintain mobility of the clawed fingers.

After three months, the streptohydrazide was replaced by Solapsone, 50 per cent aqueous solution given by injection in doses up to 1 c.c. There had at this time been marked reduction in the size and degree of tenderness of the right ulnar nerve, some resolution of the major tuberculoid lesions but no change in the claw hand.

After seven months treatment some return of movement was noted in the clawed fingers. There was still a firm fusiform swelling of the ulnar nerve just above the epicondyle but both proximal and distal to this swelling the nerve felt normal. Thiambutosine was withdrawn and treatment maintained with Solapsone 50 per cent 1 c.c. twice weekly.

After 16 months treatment, further examination showed complete recovery of the claw hand.

DISCUSSION

The recovery of function in this case after so long an interval must have been due to regeneration of nerve fibres previously destroyed by the abscess formation. It is considered that this regeneration was facilitated by limiting surgical intervention to *simple incision along the line of the nerve fibres.*

CASE II

A young adult of about 22 years who reported to a Government hospital with a patch on the dorsum of the left hand and index finger and a cord-like thickening of the cutaneous branch of the radial nerve along the dorsum of the left hand and at the left wrist. A biopsy showed small yellowish protuberances on the nerve which were, in fact, small abscesses, and a tuberculoid histology.

This patient responded very well to combined therapy with thiambutosine and 50 per cent Solapsone by injection. There was slight residual wasting of the thenar eminence and anaesthesia to contain wool touch of the thumb and index finger of the left hand.

SUMMARY

Two cases of nerve abscess are reported. In one there was complete recovery of the claw hand associated with the abscess of the ulnar nerve trunk; the other involved a cutaneous nerve only.

My thanks are due to the Chief Medical Officer of Tanganyika for permission to publish.

Reference

BROWNE, S. G. (1957). *Leprosy Review*, **28**, 20.

Hypopigmented Patches in Fundus in Leprosy

DR. S. CHATTERJEE, M.B., D.O., D.O.M.S., F.R.C.S.E., F.R.C.S.
Central Hospital, Ministry of Health, Tamale, Ghana,
and
DR. D. S. CHAUDHURY, M.B., B.S.,
Ghana Leprosy Service, Ministry of Health, Tamale, Ghana.

In a recent survey of 250 leprosy patients an unusual type of abnormality in the fundus was detected. Out of 50 examined with the ophthalmoscope four showed the abnormality and in both eyes. Two were resolved lepromatous cases and the remaining two retrogressed tuberculoid cases.

Fundus pictures of them were taken on Kodachrome II film by a Zeiss Fundus camera, and four patients showed the spots.

THE LESIONS IN THE FUNDUS

Dull, hypopigmented, flat and discrete patches of dots to one quarter of the disc in diameter were scattered all over the fundus, grouped at places but sparsely situated at the macula and extreme periphery. They were all deep to the retinal vessels and did not produce any scotoma nor field defect. The trans-illumination test was normal.

No associated pigmentation of any kind, nor haemorrhage, scarring, atrophic patches or inflammatory vitreous opacity were noted.

The appearance suggested hypopigmented spots in the choroid without inflammation.

LITERATURE REVIEW

No parallel example in English literature was found. Nodules and polypoid lesions were however described in leprosy (ELLIOT 1949; SOMERSET 1957).

It was differentiated from the following conditions:

(1) Miliary tubercules of the choroid, a severe inflammatory condition rapidly producing vitreous opacity.

(2) Disseminated choroiditis, producing white scarring, pigmentation at the margins and scotomata at the patches.

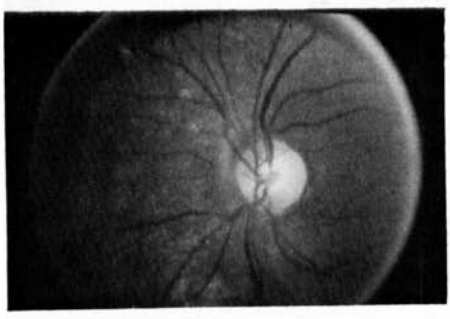
(3) Congenital multiple colloid bodies (DRUSEN) showing bright shining white dots all over the fundus (IDA MANN 1957).

(4) Colloid bodies in the choroid, as a senile or pathological change, (DUKE-ELDER 1962), showing few scattered yellow-white spots each raising the retinal pigment epithelium in front producing a pigment halo around (WOLFF 1951).

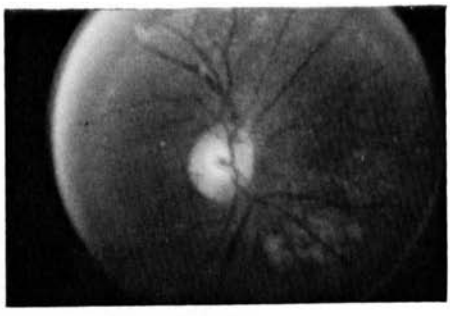
(5) Tay's central choroidal atrophy, affecting the macula with colloid bodies and producing some scotoma.

(6) Diabetic retinopathy, showing hard white dot exudates, micro-aneurisms and dot haemorrhages.

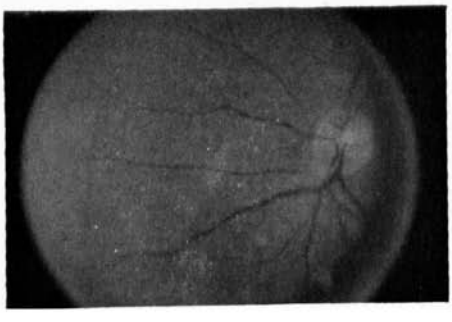
(7) Onchocerciasis, a heavily endemic disease here, which may produce



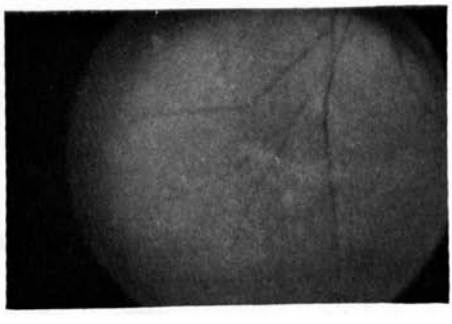
NO. 1
Hypopigmented spots in left fundus. A.D. female aged 37 years. Tuberculoid macules on back neck and chest 4 years, now healed.



NO. 2
Hypopigmented spots in left fundus. Same patient as in photo No. 1.



NO. 3
Hypopigmented spots in left fundus. E.N.B. female aged 30 years. Lepromatous Leprosy infiltrations of the body with some facial involvement, many years, now improving on treatment.



NO. 4
Hypopigmented spots in right fundus. M. M. male aged 45 years. Lepromatous Leprosy of long duration, face not involved, now improving on treatment.

fundus changes as choroidal sclerosis, retinal pigmentations (BUDDEN 1962) and white salt-like deposits (MANSON-BAHR 1961) with gross visual defect, but so far not reported to have produced pure depigmentary patches in the choroid. Moreover the skin snip test for onchocerciasis was negative in present cases concerned.

POSSIBLE RELATION TO LEPROSY

It makes more sense to think it as related to leprosy rather than a rare form of unknown congenital anomaly seen in a few leprosy patients only. On the other hand the literature reveals two facts: (1) presence of leprosy bacilli in the choroid were frequently seen in histopathological slides (PRENDERGAST 1940) even without choroiditis and (2) Hypopigmentation due to defective melanogenesis is one of the characteristics of infection by

leprosy bacilli brought about by some unknown biophysical and biochemical mechanism (KHANOLKAR 1955). These support the possibility that hypopigmented patches in the choroid are caused by slowed-down melanogenesis in the same way as it occurs in skin in leprosy.

COMMENTS

In the absence of histopathological examination the true nature of this condition remains unknown. From the appearance and by clinical elimination the disease appears to be hyopigmented spots in choroid.

Although the appearance is somewhat alarming, it is in fact a benign condition not affecting vision at all. The rest of the eye did not have any other leprotic lesion as well.

As the spots are merely a matter of colour contrast, it is pronounced and easily detected in the fundi of dark Africans.

ACKNOWLEDGEMENT

Grateful thanks are due to the Chief Administrator, Ministry of Health, for giving permission to publish this paper. Thanks are due to DR. M. SAID, Principal Medical Officer, Northern Region and to DR. B. D. MOLESWORTH, Specialist-in-Charge, Ghana Leprosy Service, for their encouragement.

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Leprotic Reactions and Anabolic and Anti-Diabetic Drugs

DR. B. B. GOKHALE
Hon. Dermatologist, Sassoon Hospitals, Poona (India)

DR. M. G. KOTNIS
Department of Dermatology, Sassoon Hospitals, Poona (India)

DR. P. V. KASBEKAR
Bio-chemistry Division, Department of Pathology, Sassoon Hospitals, Poona (India)

DR. S. V. MARATHE
Kondhawa Leprosy Hospital, Poona (India)

INTRODUCTION

One of the distressing phases of lepromatous leprosy is the lepra reaction. Some unfortunate ones get these bouts repeatedly and some others are almost continuously in reaction. Though relief can be given with treatment, it is temporary and repeated episodes of the reactionary phase progressively push the patients down hill. Lepromatous leprosy being a systemic disease M. Leprae is widely disseminated throughout the body. With such generalisation of the disease there is widespread infiltration of the skin, liver, testes, etc.

In such cases, clinically hypo-proteinemia and anaemia, are evident. Patients complain of pains and aches in the bones and joints, because during these reactions the adverse effect of leprosy on bones is at its worst (2). They often complain of testicular pain, general asthenia, and anorexia and their depressed mental state is obvious. In keeping with these signs and symptoms, the following abnormal findings are usually noted:

1. Loss of weight.
2. Reversed albumin: globulin ratio.
3. Increased Erythrocyte Sedimentation Rate (E.S.R.).
4. Decreased Haemoglobin.
5. Swelling of hands and feet.
6. Osteoporotic changes.

Lepra reaction does not seem to be a specific uniform response to one causative agent but it seems to be a response to a large number of widely differing agents. The therapeutic problem becomes more complicated and difficult because the exact nature of lepra-reaction is not clearly understood. Hence a clinician is continually hunting for better methods of relief and treatment. The present paper can be best described as a report

on such a hunt. Recently, several non-steroid compounds allied to testosterone *e.g.* *Oxymethalone, *i.e.* 17 Beta Hydroxy-2 hydroximethylene-17 alpha-methylandrostan-3 and *19 nor-androstenolone phenyl propionate **have come in use. They have a very favourable anabolic action and their androgenic effects are not as prominent (4). Therefore a wider application of these drugs even in females is possible. Pharmacologically and therapeutically they are found to be useful in conditions where there are manifestations of hypo-proteinemia as reflected by reversal of albumin: globulin ratio, oedema, decrease in body weight, asthenia, and depression etc. In leprosy subjects in question such a picture is very common, and hence one is inclined to employ these drugs in such cases as the signs and symptoms in these patients dovetail nicely with the therapeutic effects of this medication. Anapolon and Durabolin are also known to influence the calcium metabolism. This is an important therapeutic property as applied to leprosy, because it is known that derangement in blood calcium levels occurs with advanced disease (1, 3). The effect of these drugs on calcium metabolism is of greater interest now, as glucocorticoids commonly used in the treatment of lepra reaction are known to induce osteoporosis (7).

M. Leprae is known to invade the liver. Consequently liver functions are disturbed (6). Salubrious effects of anti-diabetic sulphonamide compounds on the liver function have been reported (5). Therefore in view of involvement of liver in leprosy *** D-860-Tolbutamide was added to this therapeutic study.

MATERIALS AND METHOD

Six patients of leprosy of lepromatous type have been studied. These patients were almost constantly suffering from reactions for a period varying between 2 and 5 years. Their skin smears were highly positive for *M. leprae* and the histological picture of skin biopsis confirmed the lepromatous type. They had oedema of hands and feet, which pitted on pressure. But this oedema was different from the one seen in Congestive Cardiac Failure which easily pits on pressure. All the patients were males. Their ages varied between 26 to 36 years. The general condition of these patients was poor. Two out of six cases were advanced cases and were bed-ridden (Case Nos. 1 & 2); two cases (Case No. 3 & 4) were of moderate type. Cases No. 5 & 6 were not far advanced and severity of their disease was even less than Case No. 3 and 4. Patients suffering from liver cirrhosis, cardiac and kidney diseases or diabetes were excluded. In all these patients Venereal Disease Research Laboratory test (V.D.R.L.) was negative and fasting blood sugar levels were within normal limits. Renal function tests done before therapeutic trials were within normal limits.

*Hereafter the trade names of the preparations *Anapolon and **Durabolin will be used respectively.

***Hereafter the trade name of Rastinon will be used.

METHODS

All the patients were inpatients and of a leprosy hospital†. They were transferred temporarily to a general hospital for laboratory investigations‡. Following investigations were carried out in each case:

1. Height and weight.
2. Haemoglobin, Erythrocyte Sedimentation Rate (E.S.R.) White blood cell count, total and differential.
3. Urine examination: Specific gravity, phenolsulphonphthalein test, albumin, sugar, microscopic.
4. Electrolytes – Sodium and Potassium levels in blood.
5. Liver function tests.
6. Liver biopsy.
7. Fundoscopy of eyes.
8. X-ray pictures of hands.
9. Biopsy of lepromatous lesions of the skin.
10. V.D.R.L. (Test at the Venereal Disease Research Laboratory for Syphilis.)
11. Fasting blood sugar level.
12. Skin smears for *M. leprae*.

These patients were put on the following therapeutic regime:

1. Anapolon 50 mg./day orally in two divided doses.
2. Injection Durabolin 25 mg./Intramuscularly once a week.
3. Rastinon 500 mg./day orally in two divided doses.

Case No. 1 was administered injection Durabolin only all along the course of the treatment. All the other five patients were given Anapolon for a period of first three months. Later they were put on injection Durabolin during the rest of the treatment schedule.

The following drugs were used as and when required. Gluco-corticoids trivvalent antimony compounds, Vit. B. Complex, Vit. C, Iron, Glucose, calcium, either orally or parentarally. Such supportive treatment was found to be of not much use prior to the use of the drugs under trial. These patients were given high protein diet in the form of milk reinforced by milk powder and eggs, in addition to their routine hospital diet.

RESULTS

The results of these investigations are given in the accompanying tables. It is obvious from Table No. 1 that all the patients have put on weight. There was an improvement in general health. They had a sense of well being. Those that were bed-ridden became ambulant (Case No. 1 & 2). However case No. 1 deteriorated during last three months. There is decrease in E.S.R. in all the cases except Case No. 4. Haemoglobin percentage and red blood cell counts have improved in all the patients except Case No. 3. The X-ray pictures of the Cases No. 5 and 6 showed fair amount of recalcification and arrest of atrophic changes. No such changes were observed in other patients (Table 2). During the first three months of trials there was an impression that the frequency of lepra reactions was

TABLE 1

Date	Height	Weight Lbs.	Liver function tests T.P.	Alb.	Glo.	1	2	B	r
Case No. 1									
24.11.62	5′–6½″	93	6·7	2·3	4·4				
18.3.63		98	8·35	2·6	5·7	0·78	1·03	1·13	2·4
21.9.63		100	5·5	1·39	4·11	0·91	0·49	1·08	1·83
Case No. 2									
2.1.63	5′–3½″	94	6·8	2·8	4	0·78	0·9	1·0	1·84
18.3.63		98	8·35	1·85	6·5	0·8	1·8	1·4	2·5
27.8.63		102	7·65	2·52	5·13	0·5	1·1	1·3	2·2
Case No. 3									
25.1.63	5′–6¾″	112	7·4	2·9	4·5	0·4	0·9	1·1	2·3
4.4.63		119	7·2	2·44	4·76	0·84	1·05	1·05	1·84
21.9.63		114	5·3	2·4	2·9	0·15	0·22	0·79	1·74
Case No. 4									
25.1.63	5′–1¾″	108	7·9	2·63	5·27	0·51	1·02	1·15	2·59
4.4.63		118	8·1	3·43	4·68	0·81	0·86	1·04	1·96
6.9.63		115	6·7	3·1	3·6	0·26	0·55	0·83	1·01
Case No. 5									
22.12.62	5′–3″	93	6·75	3	3·75	0·7	1·0	1·15	2·0
18.3.63		114	7·65	2·82	4·83	0·79	0·85	1·0	2·04
6.9.63		121	7	3·30	3·70	0·33	0·63	0·94	1·80
Case No. 6									
22.12.62	5′–6¼″	93	7·0	3·18	3·82	0·79	0·7	1·0	2·0
18.3.63		107	7·65	2·75	4·9	0·73	0·73	1·1	2·34
6.9.63		118	6·5	2·5	4·0	0·76	0·76	0·7	2·27

1 : *alpha one globulin*
2 : *alpha two globulin*
B : *Beta globulin*
r : *Gama globulin*

TABLE 2

Date	*E.S.R. mm./hr.*	*Hb. Gms. %*	*R.B.C. million c.m.m.*	*X-ray report of hands*
Case No. 1				
24.11.62	44	6	3	There is no improvement
18.3.63	38	8	3	or
21.9.63	30	9	3·5	restoration of cal. content of bone
Case No. 2				
2.1.63	44	8·5	2·8	
18.3.63	36	9·5	3	There is no improvement
27.8.63	32	9·5	3	
Case No. 3				
25·1·63	12	12	3·8	
4.4.63	5	12·5	4	There is no improvement
21.9.63	8	10·5	3	
Case No. 4				
25.1.63	20	9	3·4	
4.4.63	10	10	3·8	There is no improvement
6.9.63	28	10	4	
Case No. 5				
22.12.62	36	7	3·5	De-calcification changes. No atrophic changes.
18.3.63	28	11	4	Restoration of Ca. concent to normal level in bones.
6.9.63	26	12	4·5	
Case No. 6				
22.12.62	38	9	3	Osteoporotic changes and also atrophic changes.
18.3.63	26	10·5	3·5	Atrophic changes arrested and greater
6.9.63	30	11	3·8	amount of calcification is seen.

reduced. But at the end of this study it was found that there was no significant reduction in the number of reactions or their severity.

SUMMARY

Anabolic agents (Anapolon, Durabolin) have been therapeutically tried along with Rastinon (oral anti-diabetic agent) in cases of lepromatous leprosy.

An over-all improvement in body weight, E.S.R. and Haemoglobin percentage have been observed. In two cases recalcification of bones and arrest of process of osteoporosis is noted. Evaluation of the individual drug is indicated.

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†Dean, Sassoon Hospitals, Poona.
‡Authorities of Kondhawa Leprosy Hospital.
Organon laboratories for supplying Durabolin.
Hoechst laboratories for supplying Rastinon and Hostacortin.
Imperial Chemical Industries for supplying Anapolon.

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The Isopathic Phenomenon of Sagher Preliminary Report on Leprosy Patients in the Philippines

PERPETUA D. REYES-JAVIER, M.D., MEDICAL SPECIALIST
Division of Sanitaria, Bureau of Disease Control, Manila

The isopathic phenomenon first described by SAGHER and his associates in 1952 is the term applied to a 'specific altered tissue reactivity', as the result of which the intradermal injection of certain substances produces a histological response characteristic of the disease itself. This phenomenon is distinct from the isomorphic phenomenon of KÖBNER, in which identical skin lesions are produced on unaffected skin by any kind of injury. This phenomenon is seen in such diseases as psoriasis, lichen nitidus, verruca plana, and infectious eczematoid dermatitis[1].

SAGHER, KOCSARD, and LIBAN[2] observed the isopathic phenomenon in biopsy sections of nodules produced by the injection of tuberculin in patients with inactive lepromatous leprosy. They subsequently studied the effect of other proteins, specific and non-specific, *e.g.* leishmania, living tubercle bacilli, milk and peptone solution [3,4,5,6,7 and 8]). Their observations were confirmed by RICHTER[9], who inoculated leprosy patients with tuberculin, milk and india-ink, and by WAALER[10] who used intradermal injections of old tuberculin.

In view of the possible importance of the isopathic phenomenon, certain studies have been made on patients suffering from different kinds of leprosy, on patients with various dermatoses and on healthy contact of leprosy patients.

PATIENTS AND METHODS

A total of sixty-seven leprosy patients from the Leprosy Research and Training Centre, Department of Health, Manila, and from the Central Luzon Sanitarium, Novaliches, Rizal, were included in this study. They were grouped as follows: indeterminate, 4; typical tuberculoid, 6; tuberculoid in reaction, 18; reactional tuberculoid, 3; inactive tuberculoid, 2; maculo-anaesthetic, 5; borderline, 3; lepromatous, 15; primary polyneuritic, 11. For controls, patients with diverse dermatoses and three contacts of leprosy patients were chosen. The classification of each type was based on clinical characteristics and bacteriological examination from different sites. Clinical and pathological findings were correlated by the author.

INDETERMINATE

Clinical – one to few ill-defined smooth hypopigmented macules some of which were partially or totally anaesthetic. There was no history of previous erythema on the sites involved.

Acid-fast smears – negative.

Histopathology – perivascular lymphocytic infiltrate.

TYPICAL TUBERCULOID
Clinical – one to several circinate anaesthetic patches of various sizes with narrow, red, flat or slightly elevated borders.
Acid-fast smears – negative.
Histopathology – evidence of typical tubercles.

TUBERCULOID IN REACTION
Clinical – Few to several anaesthetic patches of various sizes, some of which showed circinate pattern, others with varying degrees of infiltration of the lesion. Some patients had nerves slightly or moderately enlarged, with or without slight to moderate tenderness.
Acid-fast smears – negative.
Histopathology – 16 of the 18 patients showed typical tuberculoid reaction; one had perivascular lymphocytic infiltrate; no biopsy was performed on the remaining patients.

REACTIONAL TUBERCULOID
Clinical – Markedly infiltrated large patches (which had been originally typically tuberculoid), and irregularly disseminated red papulo-nodules.
Acid-fast smears; + to ++
Histopathological – All 3 cases showed granulomatous foci composed chiefly of epithelioid cells and lymphocytes, although the tuberculoid pattern could be seen with difficulty in some biopsy sections. Intercellular and intracellular oedema was evident.

INACTIVE TUBERCULOID
Clinical – Hypopigmented anaesthetic patches which were previously red and elevated; with enlarged non-tender nerves supplying the involved site.
Acid-fast smears – negative.
Histopathological – perivascular lymphocytic infiltrate.

MACULO-ANAESTHETIC
Clinical – Multiple hypopigmented large smooth anaesthetic macules with atrophy and/or contractures of the muscles of one or more limbs.
Acid-fast smears – negative.
Histopathological – perivascular lymphocytic infiltrate in one patient; no biopsy was performed on two patients.

BORDERLINE
Clinical – Generalized coppery-red papulo-nodules, with borders not well-defined. One patient developed erythema nodosum during treatment.
Acid-fast smears; ++ to +++
Histopathological – non-specific granulomatous infiltrate.

LEPROMATOUS
Clinical – Generalized infiltrated yellowish-red patches and papulo-nodules; some, with leonine face, madarosis and enlarged ear-lobes.
Acid-fast smears – markedly positive.
Histopathological – not done.

PRIMARY POLYNEURITIC
Clinical – no skin lesions either at the time of examination or before. Some showed either atrophy or contracture or both while others had anaesthetic patches.
Acid-fast smears – negative.
Histopathological – seven patients showed no tissue reaction in sections from anaesthetic areas; in four patients biopsy was not performed.

The materials used for intradermal injections were: triple-distilled water; peptone solution (1–5 per cent), 'Bear Brand' milk (0.1 per cent); and lepromin (prepared by Mabalay of Eversley Childs Sanitarium, Cebu, Philippines); about 0.1 ml. of the test solution was injected intradermally on the antero-medial aspect of the thigh. For comparative studies, some patients received several tests. When multiple tests were done on the same patient, the antigens, including lepromin, were either given on both thighs at symmetrical sites, or the skin tests were done 1–2 cm. apart on one thigh. The test sites were marked by silver nitrate solution (10 per cent) drawn 2–3 mm. around the point of injection. All the skin tests including lepromin were read after three to four weeks and recorded according to the following notation: doubtful (1–3 mm.); + (3–5 mm.); ++ (5–10 mm.); +++ (more than 10 mm.) or less if there was ulceration. To study the effect of trauma, a dry 24-gauge needle was used.

HISTOLOGICAL EVALUATION OF THE SKIN TEST SITES

In the indeterminate and maculo-anaesthetic forms of leprosy, the tissue response at the inoculation sites was that of non-specific banal inflammatory infiltrate, chiefly perivascular. perineural, or peri-adnexal. In some instances, a few epithelioid cells were found at the centre of the lymphocytic foci. The tuberculoid tissue response was characterized by granulomatous foci, discrete or coalescent, predominantly of epithelioid cells and lymphocytes in different proportions, and in some cases of one or more giant cells of Langhan's type. The common tissue response consisted of a tubercle composed of centrally grouped epithelioid cells surrounded by a zone of lymphocytes. In inactive lesions the tuberculoid element had disappeared, and only perivascular lymphocytic infiltrate was found.

SUMMARY OF OBSERVATIONS

TISSUE RESPONSE IN SITES INOCULATED WITH DISTILLED WATER AND LEPROMIN SIMULTANEOUSLY

1. **Tuberculoid leprosy** – (20 *patients – various types:*
Lepromin: tuberculoid response (19 patients); non-specific granuloma (1 patient).
Distilled water: tuberculoid response (15 patients): non-specific granulomatous infiltrate or perivascular banal inflammatory infiltrate (4 patients); no response (1 patient).
2. **Primary neural leprosy** (11 *patients):*
Lepromin: tuberculoid response (6 patients): non-specific perivascular round-cell infiltrate (1 patient); 4 patients were not given lepromin.
Distilled water: tuberculoid response (5 patients): perivascular lymphocytic infiltrate (6 patients).
3. **Indeterminate leprosy** (3 *patients):*
Lepromin: tuberculoid response (3 patients).
Distilled water: tuberculoid response (1 patient); no response (2 patients).
N.B.—All these patients subsequently developed tuberculoid features clinically.
4. **Maculo-Anaesthetic leprosy** (2 *patients):*
Lepromin: tuberculoid response (2 patients).
Distilled water: tuberculoid response (1 patient); no response (1 patient).
5. **Borderline leprosy** (3 *patients):*
Lepromin: non-specific granuloma (1 patient); no reaction (2 patients).
Distilled water: perivascular lymphocytic infiltrate (2 patients); non-specific granuloma (1 patient).
6. **Lepromatous leprosy** (5 *patients):*
Distilled water: lepromatous response (4 patients): perivascular lymphocytic infiltrate (1 patient).
Lepromin test: not done.

TISSUE RESPONSE IN SITES INOCULATED WITH PEPTONE SOLUTION AND LEPROMIN SIMULTANEOUSLY:

1. **Tuberculoid leprosy** (12 *patients, various types):*
Lepromin: Tuberculoid response (9 patients); perivascular lymphocytic and granulomatous response (2 patients); 1 patient was not given lepromin.
Peptone: tuberculoid response (5 patients) banal inflammatory infiltrate (2 patients); no tissue response (5 patients).
2. **Primary neural leprosy** (6 *patients):*
Lepromin: tuberculoid response (2 patients); 4 patients were not given lepromin.
Peptone: tuberculoid response (4 patients); non-specific banal inflammatory infiltrate (2 patients).
3. **Indeterminate leprosy** (1 *patient):*
Lepromin: tuberculoid response.
Peptone: perivascular lymphocytic infiltrate.
4. **Borderline leprosy** (3 *patients):*
Lepromin: non-specific granulomatous response (1 patient); no response (2 patients).
5. **Lepromatous leprosy** (5 *patients):*
Peptone: lepromatous response (3 patients); no response (2 patients).
Lepromin: not given.

TISSUE RESPONSE IN SITES INOCULATED WITH MILK AND LEPROMIN SIMULTANEOUSLY:

1. **Tuberculoid leprosy** (3 *patients):*
Lepromin: tuberculoid response (2 patients); perivascular lymphocytic infiltrate (1 patient).
Milk: tuberculoid response (2 patients); perivascular lymphocytic infiltrate (1 patient).
2. **Primary neural leprosy** (4 *patients):*
Lepromin: tuberculoid response (2 patients); non-specific banal inflammatory infiltrate

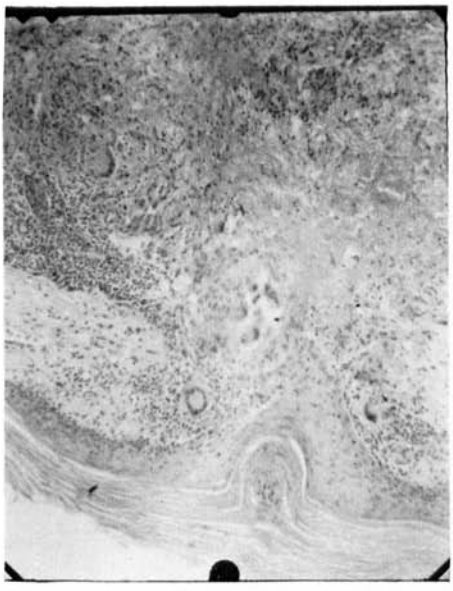

FIG. 1. Site injected with distilled water in a patient with tuberculoid leprosy, showing the typical tuberculoid features of the tissue reaction. 2600 ×

FIG. 2. Site injected with peptone solution in a patient with primary neural type of leprosy showing the tuberculoid histology of tissue reaction. 2600 ×

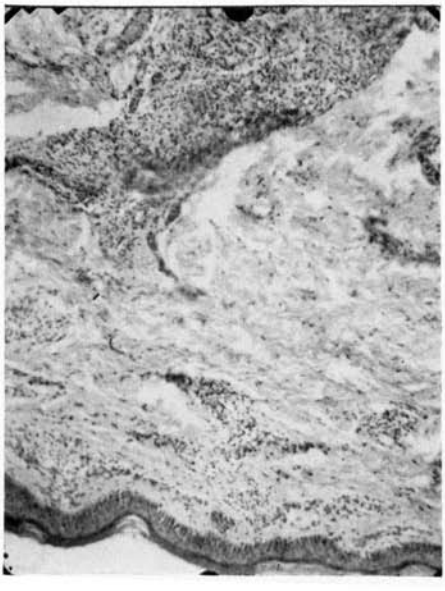

FIG. 3. Site injected with distilled water in a patient with lepromatous leprosy showing focalized lepromatous tissue in the superficial dermis and massive granuloma in the deeper layers.

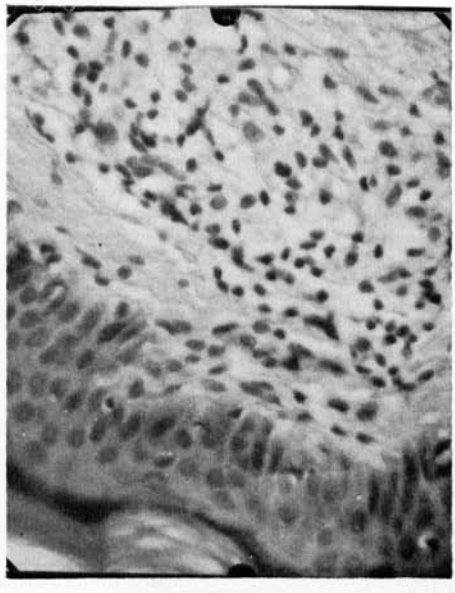

FIG. 4. High power magnification of a part of the skin in Fig. 3 showing the foam cells. 12, 350 ×

(1 patient); 1 patient was not given lepromin.
Milk: tuberculoid response (1 patient): perivascular lymphocytic infiltrate (3 patients).
3. **Indeterminate leprosy** (3 *patients*):
Lepromin: tuberculoid response (3 patients).
Milk: perivascular lymphocytic infiltrate (3 patients).
4. **Maculo-anaesthetic leprosy** (1 *patient*):
Lepromin: tuberculoid response.
Milk: tuberculoid response.
5. **Lepromatous leprosy** (1 *patient*):
Lepromin: no tissue response.
Milk: perivascular lymphocytic infiltrate.

TISSUE RESPONSE TO TRAUMA:
Tuberculoid leprosy (3 *patients*):
Lepromin: tuberculoid response (all 3 patients).
Response to trauma: no response (all 3 patients).

TISSUE RESPONSE TO LEPROMATOUS PATIENTS TO LEPROMIN ALONE: (5 *patients*):
Lepromatous response (4 *patients*):
Tuberculoid response: (1 patient).

TISSUE RESPONSE IN PATIENTS WITH VARIOUS DERMATOSES
Patients suffering from the following dermatological conditions were selected for intradermal injections: pityriasis rubra pilaris, granuloma annulare, discoid lupus erythematosus, lupus verrusosus cutis and post-encephalitic claw-hand. No recognizable tissue reactions were obtained at sites injected with peptone, distilled water, milk and lepromin, with the sole exception of the tuberculoid response at the site of lepromin injection in the patient with granuloma annulare reported by the author (11) whose lesion on the right wrist was anaesthetic for a period of six months.

TISSUE RESPONSE IN HEALTHY CONTACTS OF LEPROSY PATIENTS
Of the three contacts of patients with leprosy who were tested by intradermal injections of water, milk and lepromin, one gave a tuberculoid response at the sites of injection of water and lepromin; another showed a similar response at the site of the lepromin injection alone, while the third patient showed tuberculoid features at the sites of the milk and lepromin injections.

SUMMARY

1. Histological reactions of typical tuberculoid granulomatous aspect were seen in majority of patients with tuberculoid leprosy, irrespective of the precise kind of tuberculoid disease they were suffering from and irrespective also of the nature of the substance injected.
2. In primary neural leprosy, most of the test sites that were strongly positive showed tuberculoid histology, and most of the test sites that were negative showed perivascular lymphocytic infiltrate.
3. Patients with indeterminate and maculo-anaesthetic leprosy showed tuberculoid response at the test sites, specially noticeable at the sites where distilled water had been injected.
4. In borderline and lepromatous leprosy, non-specific granulomatous infiltrate and lepromatous changes were observed respectively at the test sites.
5. The fact that trauma by itself failed to elicit a typical tuberculoid response suggest that some substances must be introduced intradermally in order to excite the corresponding tissue reaction.
6. Patients with diverse dermatoses failed to give recognizable tissue response at the test sites.
7. Some contacts of patients with leprosy showed a tuberculoid response at the sites where water, milk or lepromin had been injected.
8. Distilled water injections showed the most typical tissue reaction in this experiment.

9. Injection of lepromin evoked a typical example of the phenomenon of SAGHER.
10. No definite conclusion can be made on the advantage or disadvantage of the injection of test substances on the same or both thighs, due to variability of results.

In intradermal injections of different test substances on opposite thighs at symmetrical points, 72 per cent gave similar tissue reactions, while the remaining 28 per cent gave diverse pathological findings. In patients where multiple tests were done on the same thigh, only 17 per cent of the cases gave similar tissue response at the various test sites.

CONCLUSIONS

Further studies of SAGHER's phenomenon should be undertaken in view of its possible bearing on immunology in leprosy. In particular, latent leprosy with no cutaneous lesions might be detected by this means, for example among contacts and spouses.

Again, the type of leprosy might be indicated on histological grounds in patients whose clinical lesions though due to leprosy are typical in nature and insufficient for purposes of classification.

ACKNOWLEDGEMENT

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A New and Simplified Technique of Treating Acute Neuritis in Leprosy, Using Ethyl Chloride Spray

DR. DOUGLAS E. HENRY, B.SC., M.B.B.S.,
The Mission to Lepers, Chandkhuri Leprosy Hospital and Homes,
P.O. Baitalpur, via Bhatapara, M.P. India

INTRODUCTION

Swollen and painful nerves are fairly frequently found as an annoying complication in the course of leprosy. The nerves most commonly affected are the subcutaneous nerves like the ulnars, the lateralpopliteals and the posterior auriculars in their order of frequency. They not only give excruciating pain and discomfort to the patient but are also responsible for taking these poor people out of work and later are responsible for the development of deformities like clawhands and dropfeet. This is due to the destruction of the nerve fibres which causes the paralysis of the respective muscles.

PATHOLOGY

It has been shown by KHANOLKAR that the nerve tissues are very susceptible to leprosy bacilli which can be found in large numbers even in the nerves of those patients who do not show the bacteria in the skin smears.

The blood and lymph supply of the nerve bundles occurs between the epineurium and the perineurium.

In the course of leprosy these venules and lymphatics are first blocked by the bacteria and because the pressure is more in the arterioles more blood comes in and stagnates. Gradually the pressure here increases to such an extent that there is resultant partial ischaemia of the nerve bundles.

D. BROWN has shown that this partial ischaemia causes a reversible paralysis or loss of conductivity without Wallerian degeneration. If blood again returns to the tissues conductivity also returns. But if the ischaemia is of long duration or if it is absolute then the nerve becomes destroyed and fibrosis take place. The paralysis then is irreversible.

During these episodes the nerves are swollen and tender.

COMMON FORMS OF TREATMENT EMPLOYED

(1) In early and less severe cases general treatment for reactions usually gives relief.

(2) Injection of novocain or lignocain with or without cortisone around the nerve sometimes gives relief.

(3) Recently novocain or lignocain with cortisone and hyalase have been injected intraneurally and have been found quite effective.

(4) Heat has been used in the form of hot compresses, diathermy or wax baths with varying amount of success.

(5) Surgery: Nerve stripping or nerve decompression are also used with varying amount of success.

OUR SIMPLIFIED TECHNIQUE

With the increase in the use of cold instead of heat in the modern therapy, we thought of using a cooling agent for the treatment of acutely swollen and tender superficial nerves.

We found that the simplest thing we could lay hold on was ethyl chloride spray. This is cheap, safe and simple. The pain is almost immediately relieved and the patients are quite thankful and return soon to their regular work.

Ethyl chloride is sprayed from a fine nozzle on the tender nerve from a distance of about 20 to 30 cm. so that about 5 to 10 cm. of the skin just over the nerve is thus treated till a fairly good coat of fine ice is formed and remains for about 1 to 2 minutes.

This procedure, if required, is repeated on the 3rd and 5th day and usually 1 to 3 applications are quite enough. No bandage is applied and the patient is asked to report as soon as he or she notices more swelling and pain, and this procedure could be safely repeated. If there is accompanying reaction then it is treated on usual lines and apart from some Asprin tablets for a day or two nothing else is given as medication.

RESULTS OF OUR TRIALS

So far we have treated 25 patients by this method and have found Ethyl chloride spray very useful in 23 cases. There were two failures but one was due to long standing neuritis and had plenty of fibrosis and one was a case having nerve abscess; for these surgery had to be applied.

COMMENTS

Twenty-five is a very small number and we are going ahead with this experiment. I feel that a properly organised drug trial will be of immense value.

Since Ethyl chloride is cheap and effective and can be used even in simple and primitive field conditions, it has a very good future in the treatment of acute neuritis.

It is also of much use in acute fibrofasciitis like wryneck and pulled dorsal muscle.

Though I have not worked out fully the pathology involved after the use of Ethyl chloride spray yet I feel that in some way the vicious cycle of increase in the pressure in the space between the epineurium and the perineurium is broken and ischaemia to the nerve bundles is relieved, which is responsible for the reduction in swelling and tenderness of the nerves. I feel this requires complete study in a big centre with all laboratory facilities.

SUMMARY

(i) Acute neuritis in leprosy is discussed including its pathology and treatment.

(ii) A new technique of treating acute neuritis in leprosy by the use of ethyl chloride spray on the skin over these nerves is described. It is assumed that cooling agents may be of more benefit to mankind than hitherto thought.

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Leprosy in Society
II. The Pattern of Concept and Reaction to Leprosy in Oriental Antiquity

OLAF K. SKINSNES, M.D., PH.D.*

A prior communication SKINSNES (1964), reporting on an inquiry into the social pathology of leprosy in South China, drew from folklore and tradition concepts which lay the groundwork for the thesis that leprosy is unique in the social opprobrium that it engenders, and that this social accretion is generated by the nature of the disease itself and is not essentially attributable to Biblical mistranslation or other specific tradition or writing. The social reaction is itself a malady, rooted in misconception and having tendrils extending into antiquity. Its cure can reasonably be expected to lie in exposure to an understanding of reaction causality coupled with the increasing effectiveness of advances in treatment.

In comparing the history of the social reaction to leprosy in Eastern and Western (including Middle East) cultures, certain parallel misconceptions and reactions appear. These tend to support the premise that the reactions have their origin in some unique intrinsicality relating to leprosy and that the Hebraic reaction to 'tsara'ath' as recorded in the Bible is not so much causative of the social reaction to leprosy as it is a reflection of a response to this unique pathological complex.

It will be suggested that the presence of a somewhat characteristic pattern of social reaction may therefore be evidence of the historical presence of leprosy, alone or together with complicating similarities in other diseases, even though clinically identifying description may be wanting, obscure, or inadequate as evidence.

EVIDENCE OF LEPROSY IN CHINESE ANTIQUITY

Chinese literature, both medical and otherwise, with reference to leprosy is inadequately recognized. Western references turn most commonly to the early study by WONG (1930), subsequently incorporated in the *History of Chinese Medicine* by WONG and WU (1936). MAXWELL (1928) referred to an early paper by EDKINS (1891) which contained material similar to that presented by WONG. More recently LAI (cā 1954) issued in mimeograph form (in Chinese) a summary of references to leprosy culled from readings in old Chinese medical literature over a period of twenty-five years. To this the writer, having caused a translation to be made,[1] is indebted for additional information.

*Department of Pathology, University of Chicago, Chicago, Illinois, U.S.A.

[1]Appreciation is expressed for expert and conscientious assistance in preparing translation and transcription on the part of Mrs. Paul Yap, neè Rosalie Leung, of Hong Kong.

WONG (1930) lists fifteen Chinese synonyms for leprosy culled from the Chinese medical literature, the individual works cited being traditionally dated from as early as 1,000 B.C. to the last noted from 1744 A.D. He concludes that though the term 'lai' in modern usage designates a group of skin diseases such as psoriasis, eczema, impetigo, scabies, etc., in times past it was used synonymously with 'li', 'lieh', and 'wu chi' as a designation for leprosy. Following on this conclusion he indicates that most Chinese commentators hold that Pai Niu, a disciple of Confucius, did have leprosy ('lai') and that this represents the first recorded instance of this disease in Chinese history. The reference to Pai Niu's illness is found in the 'Analects' (6th century B.C.) and the pertinent statement reads: 'Pai Niu is sick. The Master went to see him, and holding his hand through the window, exclaimed, "Fate kills him. For such a man to have such a disease! For such a man to have such a disease!" '

An earlier reference to the disease (EDKINS, 1891; WONG, 1930) is found in records of the Chou Dynasty (1122–256 B.C.) known as 'The Warring States'. In the chapter called 'Calendar of the Seasons' (*Yue Ling*) appearing in the *Li Ki* section of this work, it is said that 'if in the middle month, of winter the proceedings of government proper to spring were observed locusts would appear and work harm, springs would all become dry, and many of the people would suffer from the itch and from leprosy.' The import of this statement in its context is that improper government will result in disasters, and leprosy is already recognized as a disaster and is here implied to result as a punishment for moral evil. Astrological observations in this work coincide with known star positions in early Chou times. The book as a whole, however, seems to belong to an age some centuries later, perhaps about 800–700 B.C.

Even if it is allowed that these ancient records referred to the term now used for leprosy 'lai' or 'wu chi', inquiry must be made as to the characteristics of the ancient disease and its relationship to leprosy as now known.

The *Nei Ching* ('Cannon of Internal Medicine') is the oldest Chinese medical classic. The traditional attribution of its authorship to Huang Ti, 2698–2598 B.C., is historically unsupportable. WONG MAN (1950) gives reasons for attributing the work to the period 479–300 B.C. and suggests that it was then subjected to several major revisions, notably in the 2nd century B.C., again shortly after 150 A.D., yet once in the edition of 762 A.D. (still surviving), and finally the imperial edition of the Sung Dynasty, prepared in A.D. 1069–1078. Despite the later alterations it is evident that the work reflects the earliest concepts of Chinese medicine available. As it is now found, this work is in two parts, the *Su Wen* ('Plain Questions' consisting of 81 chapters) and the *Ling Shu* ('Spiritual Gate', or a classic of acupuncture, also consisting of 81 chapters). Unfortunately, no translation has been made of the whole work and the translated portions (VEITH 1949; WONG MAN 1950) do not include those germane to the present argument. However, the following three statements from this work contain descriptive elements consistent with the findings in leprosy:

'In a leper the air is not clear, thus causing the nose to *rot and the skin to become ulcerated.*'

'The symptoms of Ta Fung, now called Lei Fung, is *the falling of hair, eyebrows and beard and the swelling of joints.*'

'Acupuncture is only applied on the diseased parts of the *flesh which have lost all sensation of feeling.*' (This instruction is given in speaking of the acupuncture therapy of 'Lei Fung').

Subsequently, successive medical works add to and reiterate these observations. Thus the Pien Ch'iao Hsin Shu ('Pien Ch'iao's Classic') of about 255 B.C., states that leprosy may be caused by sleeping on wet ground on a summer night, or by evil air entering the body after sexual congress thus causing both eyes to swell and '*the skin is numb and senseless and the flesh ulcerated.*' In the preface of the Chia I Ching ('Acupuncture Classic') by Huang Fu-mi (215–282 A.D.) there is a paragraph stating that when Wang Chung-suan was twenty years old, Chung-ching (*i.e.* Chang Chung-ching, *circa* 190 A.D.) said to him, 'You are suffering from a disease which will cause your eye-brows to fall when you are forty, and death will follow in half a year's time.' Chung-suan did not believe the famous physician and ignored his medical advice. After twenty years his eyebrows fell, and death followed in 187 days. In addition to the loss of eyebrows, the chronicity of the disease process seems here to be recognized.

In the famous classic, *Shang Han Lun* ('Essay on Typhoid' originally titled 'Essay on Typhoid and Miscellaneous Diseases Combined') by the same Chang Chung-ching just referred to, it is stated that a person having leprosy has very little hair and eyebrows left and that his body is full of sores which have a fishy and stinking smell.

In the *Hua T'o Sen Yi Pei Fang Ta Chuen* ('Complete Secret Remedies of Hua T'o') attributed to the pre-eminent surgeon Hua T'o (2nd–3rd century A.D.; born *circa* 190 A.D.) there is an extended series of observations on leprosy as follows:

'*Tai Ma Fung:* The symptoms may first appear on the skin but the poison is actually stored in the internal organs. The skin is first numb without sensation, gradually red spots appear on it, then it is swollen and ulcerated without any pus. And later the disease develops to such an extent that the eyebrows fall, the eyes may become blind, the lips deformed and the voice hoarse. The patient may also experience ringing in his ears and the soles of his feet develop rotted holes; his finger joints may become dislocated and the bridge of his nose flattened.

'*General Lai:* All forms of leprosy result from evil air or from having provoked the deities. At first the skin is senseless, but gradually it becomes itchy as if something is running underneath. It should be treated immediately.

'*Black Lai:* The patient who suffers from this disease will find his voice hoarse, his vision blurred, all four limbs numb without sensation and then white spots appear in the skin. The pupil of his eye is gradually covered with white matter and gradually all vision is lost.'

Ko Hung (A.D. 281–361) was an eminent Taoist concerned with therapy of disease as well as with experimentation with the 'elixir of life'. In volume 5 of his work the *Chou Hou Pei Chi Fang* ('Prescriptions for Emergencies'), speaking of 'Lai Ping Fang' (leprosy) there is the statement: 'At first the skin is senseless; gradually there is itching as if insects are moving underneath, and the vision becomes blurred and purplish-black swellings are found in the skin.' In another work, *Kan Ying Shen Sien Chuan* ('Impressions from the Lives of the Immortals') by the same author it is recorded that a military officer named Tsui Yen was suddenly afflicted with a disease. His vision became so blurred that he could not see anything farther than a foot away, his hair and eyebrows fell, his nose became deformed, and his body was covered with sores. Everyone said that he had an evil disease that could not be cured. An unidentified Taoist (it should be borne in mind that as an ardent Taoist himself, the writer was not adverse to promoting Taoism) gave the patient a prescription consisting of a mixture of *Gleditschia sinensis* (containing Gleditsaponin; traditionally a treatment in China for lupus and scrofula) and *Rhem officinale* (active ingredient Chrysophanic acid, traditionally used as a laxative). After this treatment, it is reported, the patient's hair grew again and he was considered cured.

The epoch of Chinese history (280–589 A.D.) lying between the end of the period of the 'Three Kingdoms' and the beginning of the Sui Dynasty was an era of confusion and political disunity with many small contending states. Little of significance is recorded of the medical history of the period.

In the Sui (589–618 A.D.) and T'ang (618–906 A.D.) Dynasties several important medical works were produced by famous physicians. Among the most prominent of these was Ch'ao Yuan-fang who was imperial physician during the reign of Sui Yang Ti (605–616 A.D.). By imperial command he headed a committee of doctors which wrote an extensive treatise consisting of fifty volumes divided into sixty-seven headings and containing 1,760 chapters. This was the *Ch'ao Shih Chu Pin Yuan Hou Tsung Lun*, popularly known as the *Ch'ao Shih Pin Yüan* ('Ch'ao's Pathology') and published in 610 A.D. It says of leprosy:

'All kinds of leprosy result from evil wind. In the beginning the skin loses sensation; gradually the patient feels worms moving under his skin, then his vision becomes obscure. This disease should be treated at its very beginning'.

'The symptoms of this disease in the early beginning are not noticeable, but if not treated in time the person may find himself unable to perspire, his four limbs ache, and his whole body tingles. If he scratches, sores may be formed. Or he may be unable to move his four limbs, his eyes swollen, his urine reddish yellow and his face pallid. If the poisonous worms eat the person's liver his eyebrows will fall off, if they eat the lungs the bridge of his nose will be deformed, or little lumps of flesh will grow in the nostrils thus causing difficulty in breathing; when they eat the spleen the voice becomes hoarse; when they consume the kidneys the ears will ring with

drumming noises; if they destroy the muscles the joints will be dislocated; when they attack the skin and flesh the patient will not feel pain.'

Sun Szu-moh (died 682 A.D.) was another great physician of the T'ang Dynasty. His most famous work is the *Ch'ien Chin I Fang* ('Thousand Golden Remedies'), in volume 23 of which, under the title 'Loathsome Sickness of Leprosy', there is a special chapter on leprosy. It states, in part:

'There are many different kinds of Tai Feng (leprosy): some find themselves in a perfectly healthy state save that they have no hair or eyebrows while some find their hair and eyebrows in good condition but their bodies deformed. Some suffer from such severe chill that heavy furs cannot warm them; but some suffer from fever so severe that nothing can cool them. Some suffer severe pain due to the sores covering their bodies. Of all of these types of leprous disease some can be cured easily but some cannot be cured at all and this depends on the patient, not the physician. I have treated over six hundred patients with leprosy. Some have been cured but some do not listen to my words – thus all treatment is useless to them'. The author also indicated that persons who suffer with leprosy may not live more than ten years and some die within five or six years.

The medical works of the succeeding Sung (960–1279 A.D.) and Yüan (1280–1367 A.D.) Dynasties do not apparently add anything to the concepts of leprosy noted thus far. Chu Chen-heng, who lived during the latter dynasty, wrote the *Pen-Ts'ao Yen I Pu Wei* ('Additions to Amplification of "the Herbal" ') where he grouped the manifestations of leprosy into five categories which he headed the 'Five Deaths'. These were (1) *skin death* manifested by numbness and loss of sensation; (2) *pulse death* when blood may form into pus; (3) *death of flesh* in which tissue is without pain when cut; (4) *muscle death* in which the four limbs are without strength; and in (5) *bone death* the bridge of the nose is flattened. According to this work, if any of these 'deaths' are found the disease cannot be cured. Presumably cure in this context meant restoration to normal.

With the Ming Dynasty (1368–1643 A.D.) the tempo of contact with the West began to speed up but the medical literature shows no significant Western influence and the concepts concerning leprosy did not change. Thus Liu Chun, author of the *Yu Chi Wei I* ('Valuable Principles of Disease'), in speaking of leprosy under the term 'Ta Feng' states that the patient's body is covered with sores, his hair falls out, his fingers and toes are dislocated, his nose flattened and his eyes blind. Liu believed that the cause of the disease lay in sexual excess and over-indulgence in food. The proposed treatment was for both ringworm and leprosy, so the two conditions were associated but recognized as entities.

Hsieh I, imperial physician during the reign of Cheng Te (1506–1521 A.D.), authored the *Hsieh Shih I An* ('Medical Cases of Hsieh I') which in the volume entitled 'Lei Yang Chi Yao' ('Important Facts about Malign Ulcers') dealt extensively with the treatment of leprosy. He stated, 'People with leprosy are found mostly in Honan, Fukien and Kwangtung

(provinces). The cause of leprosy may be sexual excess while in a drunken state, or evil air entering the body during bathing or mountain climbing.' Hsich I believed that if the patient's hair fell out as a first sign of the disease, the poison was in the lungs; if the face became purplish the poison was in the liver; if penetrating ulcers were found on the soles of the feet, the poison was in the kidneys; if the body was covered with sores having an appearance similar to ringworm, the poison was in the spleen; and if the eyes were first affected, the poison was in the heart.

The *Tung I Pao Chien* ('Eastern Medical Treasury'), compiled by imperial physicians of the Ming Dynasty, relates three causes of 'Ta Feng', namely: (1) the 'luck of the place' (Feng-shui), *e.g.* a grave or a house which brings bad luck; (2) direct transmission of infection from parents, husband, wife, or other members of the family; and, (3) infective fomites, such as associated with public lavatories, bedding and clothing. Chang Chieh-pin, a physician with a military background, was a leader in the Wen-pu sect of medical practice which had a considerable influence on the practitioners in the Ming and Ching Dynasties. In his book, *Pa Chen* ('Battle Array') he indicates that he did not think that leprosy could be cured by special medical prescription, but suggested that if such a sufferer could abstain from all meat and rich food, control sexual desire, and forget all earthly things while at the same time seeking treatment early in the course of the disease, he might have a chance for a cure and a long life.

The Ch'ing Dynasty (1644–1912 A.D.) produced a tremendous volume of literature including extensive compendiums with medical sub-sections such as the *K'u Chin T'u Shu Chi Ch'eng* ('Library Collections, Ancient and Modern'). This work, printed in 1726 A.D., consisted of five thousand volumes and contained three or four times as much material as the *Encyclopedia Britannica*. This period was a time of decline in indigenous medical practices. Thus, while there were medical schools throughout the empire in T'and Sung times, there now existed only the Imperial College of Physicians in Peking which concerned itself with the training of physicians for the imperial family. There being no supervision or licensure of the profession, virtually any one who would spend a short time perusing some medical work, or who inherited a few medical prescriptions, could set up practice. The better trained practitioners obtained their knowledge by serving as apprentices to established physicians and there was a strong tendency to keep medical observations and successful treatments as secrets within the clan. The most favoured practitioners were those with the longest family history in the art (WONG and WU, 1932).

Under these conditions there was little opportunity for significant medical advance, and the concepts regarding leprosy showed little change as compared to those of earlier times. A complete review of the writings of this period is not feasible but a few references will illustrate the continuing thread of thought respecting leprosy.

In the fourth year (1740 A.D.) of the reign of the Emperor Ch'ien Lung, imperial physicians of the stature of Wang Ping and Wu Chien, under

imperial commission, began the compilation of the *Yü Ts'uan I Tsung Chin Chien* ('Golden Mirror of Medicine') which was issued in 1749 A.D. It consists of two major sections, one on internal medicine and the second on general surgery. The work is predominantly a compilation of extracts, revisions, corrections and summaries of earlier medical writings. It was, however, accepted as a standard authoritative work on Chinese medicine and may therefore be regarded as representative of medical thinking at this time. The work lists three causes of leprosy: (1) climate of areas too thickly populated; (2) direct infection from persons with leprosy, or filthy conditions of public lavatories and houses, and uncleanness of bedding and clothing; and (3) neglect of personal health such as catching cold while bathing, sleeping in the open air or on wet ground so that poisonous air (mal-air) could enter the body.

Ku Shih-cheng's family had been in the practice of medicine for three generations when he completed the *Yang I Ta Tsuan* ('Complete Treatise on Ulcerative Disease') during the reign of Ch'ien Lung (1736–1795 A.D.). In this work he declares that leprosy does not manifest itself in some people till middle age, but that it does occur in adolescence and in some appears as early as in infancy. It is opined that when the disease becomes manifest during middle age its cause is probably due to over-indulgence in sexual congress thus leaving the body weak and without any resistance to disease. When leprosy appears in adolescence, Ku Shih-cheng wrote, it does so because the body is not fully developed and negligence on the part of the parents with respect to the child's health makes the body further susceptible to disease. Once leprosy develops in such an adolescent it progresses so rapidly that only four or five of a hundred so afflicted will survive. When the disease occurs in a child four or five years of age, it is further opined, the disease is even worse for then it is congenital and entirely the fault of the parents.

This review of concepts of leprosy in Chinese medical literature will be concluded without reference to later works since the purpose of this review is to examine the indigenous development of leprosy concepts without reference to more recent Western concepts. It was shortly after the time of Ch'ien Lung, in the reign of T'ung-chih, that Gerhard Armauer Hansen announced his discovery of the leprosy bacillus (1874 A.D.).

LEPROSY IN JAPANESE ANTIQUITY

The problem of leprosy in Japanese antiquity has been studied by VEITH (1947). She concluded that,

'Ancient Japanese history of leprosy is curiously similar to that of Biblical times. Like the Levites of Israel the early Shinto priests stressed above all the need for ritual purity and fought mercilessly any affliction that was considered unclean and polluting. Impurity – whether or not it was brought about through the fault of the individual – was considered a tangible manifestation of sin. Ritual impurity could be incurred in many ways, as for instance by wounding, killing, desecration of corpses, bestiality,

incest, tumors and leprosy. All these offenses and afflictions were lumped together under the term *tsumi*, or 'sin', and the offenders were placed under taboo. The early Shinto religion provided for purification rituals which in due time cleansed the sinners of their impurity. The lepers, however, whose impurity was of a concrete nature, could not return to the state of ritual purity by means of lustrations and ablutions; they remained subject to taboo for as long as their disease persisted.'

VEITH's studies drew on numerous European reports, but set out to determine if the Japanese reaction to and treatment of leprosy antedated the earliest Christian influence in Japan. She concluded that the reaction was indigenous to the extent of not having been instigated or influenced by Christian or other European influences. In the rural communities of Japan, in early times, a known case of leprosy stigmatized the entire clan (so also in China) and because of the frequent familial appearance of the disease, the Japanese from earliest times believed that it was a hereditary disease. In the case of marriage, any hereditary trace of the disease would be rigorously searched out so as to prevent marriage alliance with any one whose relatives had been victims of the disease.

Japanese culture was from early times strongly influenced by developments in China. The relationship of such influence on the elaboration of Japanese concepts of leprosy has not been reported on. Though such study would be interesting, it is not vital to the argument of this paper and will not be pursued.

LEPROSY IN INDIAN ANTIQUITY

A few striking parallels with Oriental concepts thus far noted may be drawn from the study of Indian medicine by JULIUS JOLLY (1951), supported by a few statements from JOHN LOWE (1947). References to the original Indian sources are given by these writers and will not be repeated here.

LOWE, after a critical appraisal, concluded that there is no doubt that leprosy was well known and described in ancient India, and referred to the *Susruth Samhita*, dating to about 600 B.C., as embodying traditional knowledge from still more ancient times and as referring to leprosy, including its treatment with chaulmoogra oil. He pointed out that this work describes most of the signs and symptoms of leprosy even in its milder forms and he suggested the possibility that, ' . . . in ancient times, as in the present times, leprosy in its milder forms may have been more common in India than in some other countries.' This conclusion was reached despite recognition of the likelihood that, also in ancient India, the terms used for leprosy included other dermatologic conditions such as leucoderma.

According to JOLLY, *kustha*, in general, referred to a very dangerous skin disease causing the most wretched deformation, the so-called 'black leprosy' (compare the Chinese 'black lai', above). The *Smrtis* (Indian law writings) states that sinners of the highest grade are punished with *kustha* in their future birth. The *kusthin* was not allowed to inherit (property) unless he had practised penance to remove the sin. Eighteen forms of

kustha, divided into seven major and eleven minor forms, were recognized. From the delineation of these it is clear that though the characteristics of leprosy run as a connecting pattern through them, other disease states were not always recognized as being separate entities and were often confused with leprosy. Further divisions in classification rested on the localization of the disease in one of the 'seven elements' of the body. It was indicated that when the infection affects fat in particular there is lameness of hands, inability to walk, decay of limbs, and spreading of wounds from one part of the body to another, while with involvement of bone marrow there is prolapse or decay of the nose, redness of the eyes, maggot development in the wounds, and choking of the voice. If leprosy is in the *sukradhātu* (seminal fluid) of the father and in the menstrual blood of the mother, the disease is transferred to the offspring. *Kustha* was regarded as the worst of all diseases, and one who dies of it will be attacked by it again in future births. Coupled with the above statement that sinners of the highest grade are punished with *kustha*, there is here the implication that anyone having leprosy is such a sinner. This is supported by methods of treatment which prescribed that patients should adhere to a prescribed diet, practise pious ceremonies and penance, keep hair and nails short, avoid over-exertion, intercourse with women and indulgence in flesh and spirituous drinks.

Svitra, 'white leprosy', is frequently mentioned in association with kustha as a minor disease which occurs in subsequent births as a punishment for minor misdeeds. *Kilāsa*, thought to refer to leucoderma, is closely related to *svitra* and the confusion in differentiation is thought to be with the depigmented, anaesthetic macule of leprosy since both conditions are frequently met with in India. They were regarded in the past as so difficult to distinguish that in the census of 1891 special instructions were given on this point. According to some manuscripts, *svitra* or *kilāsa* can invade the blood, flesh and fat with resultant deterioration of the condition of the sufferer. Distinction is made as to whether the hair of the lesions is white or black, those where the hair continues black being regarded as more likely to be cured. This point is of interest in view of LOWE's insistance that the description in Leviticus, chapter 13, referring to whiteness of patches of the skin and associated hair speaks to the condition described as being leucoderma.

LEPROSY IN PRE-CHRISTIAN WESTERN ANTIQUITY

The following brief resume, for comparative purposes, is primarily concerned with the reaction to leprosy in the Mediterranean area and the Fertile Crescent prior to the time that Christianity achieved social status under Charlamaign (306–337 A.D.). Up to this time, the Bible in Christian hands had scarcely enough social influence to bias Mediterranean community thought with respect to leprosy. Indeed the New Testament was formed in the latter part of this period though the Old Testament, of course, had been available in Greek and Hebrew. The Hebrews were then

a custodial rather than a missionary people, concerned with developing and maintaining their own entity against great odds and numerous conquests and exiles. Though, no doubt, their thinking entered into the interplay of the total thought of the area, perhaps especially during their period of Hellenization, it goes contrary to the reading of history to assume that their thinking so influenced the area that they can be charged with having set the tone for the reaction to disease as a whole or leprosy in particular. Later, by the time of the Mohammedan conquests, their influence (DIMONT 1962) in Arabian medicine was substantial and Arabian medicine subsequently had great influence on the development of European medicine. However, long before this, the pattern of social reaction to leprosy in the area was set.

The problems of word context relating to leprosy are just as great for the Fertile Crescent languages of antiquity as is the problem of the definitive meaning of the Hebrew 'tsara'ath.' Several words that are possible candidates for association with leprosy (OPPENHEIM 1963) are here listed:

asakku (Assyrian) – an unidentified disease having to do with uncleanness though not, according to present knowledge, necessarily referring to leprosy.

gar(a)bānu (Akkadian) – a severe skin disease given to the care of a special physician. Sometimes used to connote 'One who is guilty.' Used also in the following sense: ' . . . if a woman (who has garbānu) has given birth to a sehhānu (malformed) child, either male or female, a sinful man has had intercourse in the street with this woman.'

garābu (Akkadian) – a disease characterized by a white spot or pustule as a first sign.

epqu (Akkadian) – an odious skin disease. Children may be born with it.

epqennu (Akkadian) – literally means 'epqu-like.'

sennītu, also *sernītu* (Akkadian) – a skin disease. Entymologically related to Hebrew 'tsara'ath.' One feature of the disease was an eruption on, or discharge from, the nose.

šiḫḫat-šēri (Akkadian) – often refers to 'consumption' but the word means 'sloughing of flesh.'

šaḫaršubbŭ (Sumerian loan word in Akkadian) – literally means 'covered with dust' or 'scaly.' Sufferers with this disease were expelled from the city and the word has odious connotations as used in curses.

isrubaa = šaḫaršubbû.

saharsuppaa = šaḫaršubbû.

li'bu (Codex Hammurapi) – divorce was permitted a man if his wife had this disease, the character of which has not been established. Either men or women, however, might have the affliction.

These terms have, for the most part, been translated as representing leprosy though there is as yet inadequate clinical characterization associa-

ted with their use to make such translation secure. The uncertainty results either from the fact that in many instances insufficient material is available to delineate the disease meant, or perhaps as a consequence of available material not having been adequately correlated by persons knowledgeable in disease patterns and able to spot significant correlations while at the same time having the requisite linguistic skills.

For comparative purposes, in full recognition of possible fallacy in translation, some sources employing these words will, however, be noted.

OPPENHEIM (1956) translated fragment Sm 2073+ of the Kouyundjik collection in the British Museum, in part, as follows:

'If he eats dust: he will become decrepit, . . . he will suffer want, alienation (?) of his god is in store for him, perplexity.

If he eats dust from a corner (of the wall): . . . he will suffer want, his mind will be at peace.

If he eats the scales of a leper (saharsuppaa): . . . (he will suffer want).

If he eats sand: . . . . . .'

This fragment dates to a 7th century B.C. copy of a text from the 2nd millenium B.C. It is clear that the context in which the disease is referred to is unpleasant. It is coincidentally interesting to recall that it was noted (SKINSNES 1964) that in South China persons with leprosy have in recent times been accused of attempting to harm other individuals by causing them to unwittingly eat scales from leprous skin.

A monument found in 1930, now in the museum at Damascus, has an inscription of a treaty between KTK (identity not established) and Arpad of Syria, concluded in about 750 B.C. The translation by FRANZ ROSENTHAL, as presented in the text compilation by PRICHARD (1955) reads:

'If Matti'el breaks this treaty and . . . , his kingdom shall be a kingdom of sand, a kingdom of sand, as long as he rules . . . Everything evil on earth and in heaven and every trouble and difficulty for Arpad . . .

'(AS) this calf is slaughtered (castrated?), thus Matti'el shall be slaughtered (castrated?), and his high officials shall be slaughtered (castrated?) . . . and the wives of Matti'el and the wives of his offspring and the wives of . . . shall be leprous (saharsuppaa) . . . and Matti'el shall be . . . ' It is interesting that the Tibetans have used a similar binding curse in their treaties. The *Liao History* (EDKINS 1891, MAXWELL 1928) states that the Tibetans are revengeful, but cease attacking each other during times of mourning. When enemies were reconciled, the blood of chickens, pigs and dogs was mixed with wine and stored in a skull. While drinking the mixture, the oath was administered with these words: 'If you take revenge again, your crops will fail, your sons and daughters suffer from leprosy, your cattle will die, and serpents enter your tent.'

Further similar passages from other Fertile Crescent records, as for example the Persian, likewise bear witness to the presence of a disease carrying severe social opprobrium though the disease was not clinically defined in those early times. It was not till Roman times that leprosy was clinically defined in available records. By the same time it is clearly

associated with social opprobium equivalent to that accorded the previous undefined clinical entity.

Aulus Cornelius Celsus (*circa* 30 A.D.) recognized and wrote briefly concerning leprosy under the heading, 'Of Elephantiasis'. Translated from the Latin (LEE 1831) he described the affliction as follows:

'That disease which the Greeks call elephantiasis is very common in some countries, although scarcely known in Italy, and is of the chronic class. The whole body is affected in such a manner that even the bones may be said to be diseased. The surface of the body frequently exhibits blotches and tumours; their colour is gradually converted into a black; the surface of the skin is unequally thick and thin, hard and soft, assuming a squamous appearance; the body becomes emaciated, the mouth, the calves, and feet swell; when the disease is become inveterate, the fingers and toes are involved in the swelling, slight fever arises, which soon carries off its victim overwhelmed with so many afflictions.'

Judging from his description of the disease, Celsus apparently kept his clinical detachment from the emotional aspects of the problem of leprosy in contrast to his successor Aretaeus who reflected the attitude and concepts of the Greeks in the second century A.D. They referred to leprosy under the terms: elephantiasis, elephas, leontiasis, and satyriasis. Aretaeus wrote (ADAMS 1856):

'The disease is also called *Leo*, on account of the resemblance of the eyebrows, as I shall afterwards explain; and *Satyriasis*, from the redness of the cheeks, and the irresistible and shameless impulse *ad coitum*. Moreover it is also called the Heracleian affection, insomuch as there is none greater and stronger than it.

'Wherefore the affection is mighty in power, for it is the most powerful of all in taking life; and also it is filthy and dreadful to behold, in all respects like the wild animals, the elephants. And from the disease there is no escape, for it originates in a deadly cause . . . . .

'But the commencement of the disease gives no great indication of it; neither does it appear as if any unusual ailment had come upon the man, nor does it display itself upon the surface of the body, so that it might be immediately seen, and remedies applied at the commencement; but lurking among the bowels, like a concealed fire it smoulders there, and having prevailed over the internal parts, it afterwards blazes forth on the surface, for the most part beginning like a bad signal fire on the face, as it were its watch-tower; but in certain cases from the joint of the elbow, the knee, the knuckles of the hands and feet . . . Tumours prominent (referring to nodules in the skin), not continuous with one another anywhere, but thick and rough, and the intermediate space cracked, like the skin of the elephant. Veins enlarged, not from abundance of blood but from thickness of the skin; and for no long time is the situation of them manifest, the whole surface being elevated equally in the swelling. The hairs on the whole body die prematurely, on the hands, the thighs, the legs, and again on the pubes; scanty on the chin, and also the hairs on the

head are scarce. And still more frequently premature hoariness and sudden baldness; in a very short time the pubes and chin naked of hair, or if a few hairs should remain, they are more unseemly than where they are gone. The skin of the head deeply cracked; wrinkles frequent, deep, rough, tumours on the face hard, sharp; sometimes white at the top, but more green at the base . . . tongue roughened with vari, resembling hail-stones; not unusual for the whole frame to be full of such (and thus also in unsound victims, the flesh is full of these tubercles resembling hail) . . . eyes misty, resembling bronze; eye-brows prominent, thick, bald, inclining downwards, tumid from contraction of the intermediate space; colour livid or black; eye-lid, therefore, much retracted to cover the eyes, as in enraged lions; on this account it is named *leontium*. Wherefore it is not like to the lions and elephants only, but also in the eye-lids 'resembles swift night.' Nose with black protuberances, rugged; prominence of the lips thickened, but lower part livid; . . . ears red, black, contracted, resembling the elephant, so that they appear to have a greater size than usual; ulcers upon the base of the ears, discharge of ichor, with pruritis; shrivelled all over the body with rough wrinkles; but likewise deep fissures, like black furrows on the skin; and for this reason the disease has got the name of elephas. Cracks on the feet and heels, as far as the middle of the toes; but if the ailment still further increases, the tumours become ulcerated, so that on the cheeks, chin, fingers, and knees, there are fetid and incurable ulcers, some of which are springing up on one part, while others are subsiding on another. Sometimes, too, certain of the members of the patient will die, so as to drop off, such as the nose, the fingers, the feet, the privy parts, and the whole hands; for the ailment does not prove fatal, so as to relieve the patient from a foul life and dreadful suffering, until he has been divided limb from limb. For it is long-lived, like the animal, the elephant . . . . .

'When in such a state, who would not flee; – who would not turn from them, even if a father, a son, or a brother? There is danger, also, from the communication of the ailment. Many, therefore, have exposed their most beloved relatives in the wilderness, and on the mountains, some with the intention of administering to their hunger, but others not so, as wishing them to die.'

This quotation from Aretaeus has been presented at length because it is frequently referred to only briefly but as being generally accepted as representing one of the earliest Western clinical delineations of leprosy and because it throws light also on the social reaction to the disease at this early period. Neither its tone nor its background suggests any influence from the Bible in its conception. It would seem clear that leprosy, the same disease as now recognized, had already called forth social opprobrium similar to that to which it has been subjected even unto more recent times.

In the light of the presentation by Aretaeus it is difficult to see why some (MOISER 1961) who wish to change the name 'leprosy' should choose as a substitute 'ELEPHANTIAS GRAECORUM' if the motive is to avoid the

traditional social context of this disease and separate it from the moiety of misconceptions to which its sufferers have been subjected down through the ages.

SUMMARIZING DISCUSSION

Taken in composite, the Chinese concepts of leprosy, outlined in their historical development above, can be summarized as follows and show a strong similitude to the manifestations of leprosy as it is recognized today:

1. Extensive nodular lesions involving the skin, most prominently of face and extremities.
2. Extensive ulceration of lesions and prominent ulcerations on the soles of the feet.
3. Paralysis of extremities and anaesthesia of lesions and extremities.
4. Loss of eyebrows and hair.
5. Lesions of the nose with flattening of the nose.
6. Disease involvement of eyes with eventual blindness possible.
7. Sometimes hoarseness of voice.
8. Chronicity in terms of years (5-10).
9. Depigmentation of some lesions; erythema and hyperpigmentation of others.
10. Association with unhygienic and crowded living conditions.
11. Increased susceptibility to the disease in association with debilitation.
12. Transmission by contact with persons having leprosy.
13. Loss of sweating ability, though not specifically noted that this loss is lesion localized.
14. Susceptibility of all age groups to leprosy.

It is true, of course, that the recognition of these characteristics was diluted and interpreted in the context of associated misconceptions so that they did not have the same force of understanding that they now represent. Nevertheless, they indicate that Chinese society, from ancient times recognized as an entity the disease known in modern times as leprosy even though, as was inevitable before the dawn of bacteriological understanding, they included other conditions with leprosy to make a dermatological moiety in which the component parts were not always discernible as separate entities. Recognizable characteristics of leprosy are, however, described as early as about 500–300 B.C.

Noteworthy and interesting is the fact that what seem to be the earliest clear clinical delineations of leprosy in Greek and Chinese medicine were the descriptions by Aretaeus and Hua T'o respectively and that these physicians were approximate contemporaries.

The social reaction of the Chinese ancients was of a pattern compatible with that of the folklore of their heirs. The reaction pattern may be summarized as:

1. Leprosy was regarded with horror and its occurence was considered a major calamity.

2. The cause of leprosy was associated with sexual and other excesses, or by the entrance into the body of malign influences, such as 'mal-air'.
3. The appearance of leprosy in an individual was associated with concepts of retribution for moral delinquency provoking the deities.
4. Leprosy was considered incurable save, perhaps, by magical means or penance.
5. The clothing, bedding and discharges from persons with leprosy were considered contaminated and possible sources of infection.
6. The disease was regarded as congenital and hereditary by some and was then regarded as being due to fault on the part of the parents.

These concepts are reinforced by repeated statements that leprosy is an evil disease, that people suffering from it are morally delinquent and by references to persons with leprosy being sent to isolation in caves or other special places. The concepts are essentially the same as those previously reported (SKINSNES 1964) as current in the present-day folklore of South China.

The supplementary brief reviews of the historical patterns of concept and reaction to leprosy in Japan and India reveals that these, though not identical, are of a pattern with that of China. Likewise, evidence is noted, notably from Aretaeus, indicating that the reaction pattern of the Mediterranean area was similar. Evidence from the antique lands of the Fertile Crescent is fragmentary but, while not giving clinical evidence for the presence of leprosy, does record a reaction pattern to an undelineated disease or disease moiety similar to that noted historically in the other areas considered. This, in view of the uniqueness of the social reaction to leprosy in broad areas where leprosy is defined, suggests that the presence of similar patterns of social opprobrium to a disease may constitute evidence that leprosy was the basic object of this reaction though the disease may not be clinically defined in available records.

Surely it is evident that by the time of Aretaeus (*circa* 150 A.D.), leprosy was recognized as a clinical entity very similar to its present day pattern. Also, it is clear that by this time the pattern of social reaction to it was set in at least the eastern portion of the Greco-Roman area. It is most unlikely that the Greek Septaguint translation of the Hebrew Old Testament was responsible for this reaction. It also seems highly improbable that leprosy was non-existent prior to the time of Aretaeus and suddenly appeared as a clinical and social entity in the interval between the Septaguint translation (*circa* 200 B.C.) and the writings by Aretaeus.

A far more probable course in history, one may suggest, was the gradual isolation by astute ancients of the major irritant in the disease moiety that had from olden times been calling forth such social fear and displeasure. Other elements having been discarded, at least in part, with the growing clinical acumen, the accretion of social opprobrium fell to leprosy which was for centuries to remain a puzzling and frightening pathologic complex. Quite probably the seventy-two (MARGOLIS and MARX 1958) wise scholars who produced the Septaguint translation were 'modern' enough

to be aware of the developing medical thinking and disease delineation. Surely they were aware of the implications of the word 'tsara'ath' and, being advanced scholars, they were probably justified in choosing the word 'lepra' which was then very likely on the way to taking on the connotations noted by Aretaeus. It would seem most uncharitable and unresponsible two thousand and more years removed from the scene to accuse these advanced scholars of not being able to choose a word from their social milieu that would most closely carry the implications of so important a concept as 'tsara'ath'.

The Bible, not being a book of 'revealed' medical facts, rather than creating the social reaction to leprosy, reflected this social reaction in order to make certain theological concepts clear in terms understandable by the society in which it was put together. In the ensuing centuries these concepts of leprosy as stratified in this Scripture, as well as in other works in many lands, continued to influence society's reactions. In-so-far as the Bible carried these concepts to areas that would otherwise have no experience with or concept of leprosy, it helped to keep alive concepts of a disease for which no alternative explanation would be available till the dawn of bacteriological and pathological understanding of disease causation and pathogenesis.

If today the ancient misconceptions of leprosy as reflected in the Bible continue to plague society, the blame can hardly be laid on the shoulders of the seventy-two but must be faced up to by this same world society which today prides itself on its science-revealed understanding.

SUMMARY

A survey of Chinese medical writings indicates that leprosy was recognized in China as early as 500–300 B.C. and clinically fairly well delineated by the 2–3rd centuries A.D. Extant records further show that the social reaction to this disease was already set in this early period and that it was essentially of a pattern with that previously reported for present-day South China. The continued re-iteration and elaboration of these early concepts and reactions to leprosy through the intervening centuries, in a society far removed from influencing contact with the Bible, strongly suggests that the Bible is not essentially responsible for the creation of the social opprobrium associated with leprosy in many portions of the world. It is rather concluded that there is some unique intrinsicality relating to leprosy that makes it subject to society's opprobrium.

Comparative reference to the historical reaction to leprosy in Japan and India reinforce these conclusions. Likewise contributory are some Middle East and Greco-Roman contributions which seems to be free of Biblical influence.

Accordingly, it is suggested that the presence of a pattern of social reaction, similar to that here noted, to a clinically undelineated or undefined disease may serve as evidence that the disease in question may well be leprosy.

The problem of the reason for this remarkable reaction to leprosy in so many disparate societies, though not necessarily all, remains to be considered and will be the subject of a following communication.

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ABSTRACT

Treatment of Mycobacterial Skin Ulcers in Uganda with a Riminophenazine Derivative (B.663).
H. F. LUNN and R. J. W. REES.
The Lancet, May 1, 1964, pp. 247-249

The report of the use of a drug active against a mycobacterial disease is of great importance in therapy of leprosy, wherein the same drug has already been tried (BROWNE, S. G. and HOGERZEIL, L. M., *Leprosy Review*, 1962, 33, 6, and the same authors in the same Review p. 182). In this trial of B 663 in Uganda there was inhibition of the growths of atypical strains of mycobacteria which caused skin ulcers, and also *Myco. ulcerans* itself. The drug suppressed experimental infections with these organisms in foot-pads of mice.

A preliminary trial of B 663 was made in ten patients who had a wide variety of lesions due to atypical mycobacteria, with encouraging results at a dosage similar to that given in leprosy. It was found that when given over a long period in severe and extensive ulceration, the drug helped to prevent spread of infection, but it was slow to destroy all viable organisms.

It is hoped that operation can be avoided by its use in early cases in a wide range of cases in a country area.