

*The Quarterly Publication of  
the British Leprosy Relief Association*

# LEPROSY REVIEW

VOLUME XXXVII NO. 1 JANUARY 1966

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# LEPROSY REVIEW

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# Editorial

## LEPRA LEPROSY CONTROL PROJECT IN MALAWI

This Project of LEPRO began in the field in 1965. It has been fortunate in obtaining the essential of good quality personnel to initiate the scheme on the ground. It began in April 1965 with the placing of certain personnel on the task, viz., Dr Gordon Currie. Dr Currie was made available by the Malawi Government and Mr Drake. Mr A. H. Drake was the first direct LEPRO employee to arrive on the 3rd of April 1965. Mr J. Eldon, also a LEPRO employee, arrived on the 25th of September, 1965 to assist Dr Currie. Secondment of three African medical assistants is being arranged and housing was made possible by the purchase of a block of flats. As the Project develops it may be necessary to house a proportion of the African staff at strategic points in the Project area and not at Blantyre.

The plans for the hospital at the Queen Elizabeth Hospital Blantyre, are under way and the staff of the Queen Elizabeth Hospital and of the LEPRO Unit will be integrated as far as possible. The Physiotherapy block for the Queen Elizabeth Hospital has been planned and adequate space facilities in the new block will be secured for LEPRO patients.

The Unit has taken over 42 Government and Mission leprosy out-patient clinics at existing static centres and altogether there are now about 5,000 cases registered. This situation has given a major task in the examination and confirming the diagnosis of the cases and of medical status. This work has been very rewarding in building up a good relationship with the patients and in educating the staff of the Rural Health Centres.

A surprising number of really gross lepromatous patients are turning up which indicates that leprosy is still vigorously breeding. Child rate so far is not high. The Unit is aiming at weekly visits in circuits with the Land Rovers. Leprosy survey work has begun especially since Mr Eldon arrived.

Of BCG vaccine, 40,000 doses have arrived and the material is in cold rooms. The Unit awaits 'contact cards' before the process of beginning the vaccination. It might be possible to use spray gun technique.

Rehabilitation has been thought of and there are possibilities in this regard to be fully explored and an Orthopaedic workshop is mentioned as a possibility.

The important matter of Record Cards has taken longer than thought to make available, but the time is coming soon when Record Cards will be available in the final draft for field use.

Laboratory work has not been forgotten and will develop towards skin biopsies and histology and other technical studies. The Pathology Department of the hospital is most co-operative and it is obvious that the volume of work will grow and the LEPRO Unit should have its own technician.

The mobile circuit depends on Land Rovers of the LEPRO Unit and there is a possibility of other vehicles like the Renault 4L being useful.

Dr Currie has been truly helpful and valuable to the Project in the initial stage and now he has to retire (early in 1966). Dr B. D. Molesworth has been appointed Director and goes out to Malawi early in 1966; so there will be a short period when both men will be in the country at the same time.

# GHANA CIVIL SERVICE

**Applications are invited for the post of SENIOR MEDICAL OFFICER (LEPROLOGY) in the GHANA MINISTRY OF HEALTH.**

**Duties:** Required to take charge of the leprosy service and be responsible for the supervision of all leprosy treatment centres.

**Qualifications:** Candidates (a) should preferably possess the M.R.C.P., or a similar specialist qualification of an equivalent or comparable standard; and (b) must have gained at least seven years clinical and administrative experience in the field of leprosy. SALARY in range £2,580-£3,250 p.a.

Appointment on contract for two tours each of 15 months' duration **In addition to salary a tax free gratuity at the rate of 10 per cent of aggregate salary is payable at the end of each tour of duty, and a tax free resettlement gratuity of 20 per cent of aggregate salary is payable on the satisfactory completion of contract.** Free passages for officer, wife and up to three children under 18 years and, in addition, an education allowance for children when not resident in Ghana and attending full-time school of £100 a child for up to three children under 18 years. Accommodation at low rental. Advance for car at 5 per cent interest, and car maintenance allowance may be granted. Generous leave on full pay. Income tax at reasonable local rates.

*For application forms, please apply to:*

**The Director of Recruitment,  
Ghana High Commission,  
248 Tottenham Court Road,  
London, W.1.**

# Obituary



Dr Miguel Angel González Prendes, illustrious Leprologist of Cuba, died on the 19th of April, 1965, of a cardiac attack.

Dr César Rodríguez Expósito, the Honorary Historian of Public Health, has kindly sent information about Dr Prendes and the news of his death has been received with great sorrow by all his friends abroad as he is known to many of us ever since the V International Congress of Leprology in Havana. We personally know him and admire his work and character, knowing how he laboured all his life intensely in the campaign against leprosy in Cuba. Dr César Rodríguez Expósito has kindly sent us a photograph which we publish in this issue.

Dr Miguel Angel González Prendes was born on 29th July, 1910, in San Luis in the Province of Pinar del Río, Cuba, and had his first and secondary education in Belén College. He began his career in medicine in the University of Havana in the year 1931, and had to extend his studies in the National University of Mexico. Later, when political changes took place in Mexico he returned to Havana and graduated

Doctor of Medicine in November 1934. He studied in the General Hospital of Mexico and in the School of Health which function in the Finlay Institute of Havana. In 1944 when Professor Dr Vicente Pardo Castelló was Director of the Patronate for the Prophylaxis of Leprosy, Syphilis, and Skin Diseases, he obtained the post of Technical and Administrative Director of the National Sanatorium 'San Luis de Jagua' which was dedicated to the treatment of leprosy patients. In the year 1946, the President of the Republic, Dr Ramón Grau San Martín, nominated him as Assistant Secretary of Health and Social Assistance, and later in 1949 he was nominated Government Patron of the 'San Lazaro' Hospital of Havana which he had to abandon on 10th March, 1952, when he was accused of conspiratory activities and later detained and imprisoned, after which he occupied his post as Director of the 'San Luis de Jagua' until his death.

During 1953 he worked in the Department of Research in the University of Havana under Professors R. Márquez, and A. Curbelo.

Actually, Dr Prendes died on the 19th April of a cardiac attack in the office of the hospital 'San Luis de Jagua'.

There are 67 scientific works chiefly on leprosy published by Dr Prendes. Recently, *The History of Leprosy in Cuba* was published in 1963 by 'Carlos J. Finlay', and a wonderful account of Hansen and his work was given in the *Revista Finlay*, and by permission it was translated into English and published in *Leprosy Review*, **35**, 4, 1964.

Dr Prendes was a member of the International Leprosy Association, and as a Leprologist of world renown he was very well known and respected. The International Society of Leprosy wishes to thank Cuba for such a man and for his contributions to leprology. His character was such that many leprologists will have personal soreness of the heart at the passing of Dr Prendes and feel gratitude for having known him. Above all, his patients will echo this personal gratitude.

# Classification of Leprosy

D. L. LEIKER

*Dermatologist, Institute of Tropical Hygiene, Amsterdam,  
formerly specialist leprologist, Ministry of Health, N. Nigeria*

The three latest International Congresses of leprologists (Madrid 1953, Tokio 1958, Rio 1963) have recognised two polar types of leprosy, tuberculoid and lepromatous and one intermediate group, borderline.

These three categories faintly reflect the concept of a spectrum of clinical, immunological, bacteriological and histological signs.

Apart from these categories a group of cases with incharacteristic macular lesions, not fitting into the spectrum, called indeterminate, is recognised.

Although the basic concept of this classification is now almost generally accepted, few workers are really satisfied with its application in practice. Not a few workers have difficulties in fitting certain types of patients into this classification. Often there is agreement about the right place of patients in the spectrum, but disagreement about the designation.

The result is that considerable differences in type distribution are reported from the same area by different workers. Reports are difficult to compare unless one is familiar with the views of the investigator about classification.

The greatest differences are found in the proportions of indeterminate and 'intermediate' patients.

The less experienced worker is confused by designations such as reactional tuberculoid and tuberculoid in reaction, indeterminate and intermediate, dimorphous and borderline, which cover part of the same field but are not interchangeable. It can hardly be denied that the situation in the field of classification is still highly confusing for the average fieldworker in leprosy and rather indigestible for the general practitioner who has to deal with leprosy only incidentally and who has no time nor need for a special study of the subject.

Much can be said for a simple classification for the lay-worker and a more detailed classification for the scientific worker. It is however

doubtful that a simple classification can be designed without loss of significance. Classification should give information about important items such as infectiousness, complications to be expected, duration of treatment needed, ultimate prognosis, etc.

A division between open and closed cases has only momentary value. The open case of today may be a closed case tomorrow, and the reverse.

A division between benign and malignant is an unsatisfactory substitute for cases on the tuberculoid side and on the lepromatous side. Many tuberculoid patients truly are benign, but many of the most severely crippled patients also belong to the tuberculoid category. Lepromatous leprosy, called malignant, may be present for a decade or more, without serious complications and without producing deformity.

The fact that leprosy patients present an uninterrupted scale of all degrees of tissue resistance to *Mycobacterium leprae* means that each grouping is arbitrary and a compromise. One should not expect sharply defined groups.

It is not logical to distinguish between tuberculoid and lepromatous types and borderline and indeterminate groups. In fact all categories are groups. At most one could speak of patients as tuberculoid and lepromatous polar types, *e.g.* the small, single, rapidly selfhealing typical tuberculoid lesion and the pure, primary, diffuse lepromatous case respectively.

It is also not logical to divide the scale into a very large tuberculoid group, a very small borderline group and a large lepromatous group. The large groups thus become very heterogeneous, whereas the borderline group is restricted to a small, rather well defined section of a large intermediate (dimorphous) group.

Nor is it logical to classify together a large number of macular lesions with an entirely different evolution, but which cannot be fitted into the scale at first glance, into an indeterminate 'dustbin'.

# CLASSIFICATION SCHEME

Onset ↓ Indeterminate group							
tuberculoid inoculation lesions	High resistant tuberculoid	Low resistant tuberculoid	Borderline tuberculoid	Borderline lepromatous	Non-diffuse lepromatous	Diffuse lepromatous	Pure, primary diffuse lepromatous
TTT	TT	T	TB	BL	L	LL	LLL
varieties	macular minor major	macular minor major	maculoid minor major	maculoid infiltrated nodular	macular infiltrated nodular	macular infiltrated nodular	
natural course	selfhealing ←			→ progressive			
Mitsuda	> 8 mm	5-8 mm	3-5 mm	2-4 mm	1-3 mm	0.-2 mm	
relapse	—	±	+	++	+++	++++	
nerve destruction	seldom, always early	often, early	often, early	often, later	less often, late	not often, very late	

In the author's opinion there are advantages in dividing the scale into more than three categories. This does not necessarily make classification more difficult, but probably even more easy. A six group classification which is based upon the degree of the tuberculoid and lepromatous element does not require more insight in these elements than a three group classification does. The advantage is that if an error in classification is made in the three groups classification the consequences are serious but an error of a shift of one group to the tuberculoid or to the lepromatous side is less serious in a six group classification.

In this article no fundamental changes in the present classification are suggested. A solution is sought in a further subdivision of the scale.

For the time being, the present terminology, although not always satisfactory, is preferred to a change. The introduction of new designations may lead to further confusion and to sterile discussions. The principle behind the designation is of far greater importance than the name.

## Indeterminate leprosy

### Per de

stable, seldom bacteriologically positive, presenting flat skin lesions. The reaction to lepromin is negative or positive. Neuritic complications may develop. These patients evolve to the lepromatous type or to the tuberculoid type or may remain unchanged indefinitely (Technical Resolutions Madrid Congress 1953).

Not a few workers classify as indeterminate a large proportion of all cases which at the moment of examination present pale, flat macules only. Other workers classify only a few patients as indeterminate.

The author belongs to the latter.

Typical tuberculoid patients seldom if ever start as indeterminate. Macular tuberculoid does not need to be classified as indeterminate if due attention is being paid to definition, degree of hypopigmentation, hypoaesthesia, etc.

Diffuse lepromatous leprosy also does start as indeterminate leprosy. The individual macules may resemble indeterminate lesions, but number and distribution of the macules and the presence of positive smears of both ears are sufficiently characteristic for a lepromatous classification.

A large proportion of the 'low resistant tuberculoid' patients however start with indeterminate lesions. This is also true for borderline and for non-diffuse lepromatous leprosy. However the true nature of the condition soon becomes evident and soon the cases can be reclassified.

These three categories in which a temporary classification of indeterminate can not always be avoided from only a small proportion of the cases and they are not a sufficient explanation for the high percentages of indeterminate cases reported.

The percentage of indeterminate leprosy becomes high if quiescent and arrested patients are included. Typical tuberculoid lesions become flat, somewhat less well defined and less hypopig-

mented. The same is true for low-resistant tuberculoid and borderline patients.

If however due attention is paid to history of the lesions definition of edges, degree of hypopigmentation, surface texture (atrophy), loss of hair, loss of perspiration, degree of hypoaesthesia, etc., it is possible to decide in a large proportion of the cases whether they are at the tuberculoid or at the lepromatous side. Lesions which have healed spontaneously but after one or more years still leave conspicuous residual hypopigmentation, atrophy and hypoaesthesia and are still clearly defined are not indeterminate but obviously at the tuberculoid side. Patients with considerable nerve damage and no signs of lepromatous or borderline lepromatous leprosy also are at the tuberculoid side because the nerve damage is a sign of tissue resistance.

In our opinion the classification of indeterminate should be restricted to patients with flat lesions, not numerous, ill defined, only slightly hypopigmented, without conspicuous atrophy, little loss of hair, perspiration or sensation, without serious damage to the larger nerves and without a history of elevation of the lesions.

The lepromin reaction is weak, not negative, but also not strongly positive. Bacilli are absent or scanty on routine examination.

Thus indeterminate leprosy becomes the first stage towards a large group of cases in between typical tuberculoid and diffuse lepromatous, with a serious prognosis if not treated or inadequately treated, because of the chances of relapse and deformities.

In many instances the classification will be a temporary one. In a smaller proportion of the patients, those who heal after treatment before dissemination of the bacilli and the appearance of more and more characteristic lesions, the classification of indeterminate is permanent. Even in these patients it is often possible to determine the place in the spectrum with the aid of the lepromin test.

The difficulty of classifying cases who have not been seen in the early or active stage is fully realised, but it is regarded as more advantageous to classify these patients with or without the aid of the lepromin test, as well as possible in the spectrum, rather than to include all such patients in an indeterminate hybrid group. The chance of essential errors is reduced by a six group classification.

### *The tuberculoid group*

This group comprises cases which are truly benign and others which show a temporary tendency to progression and which have a much more serious prognosis because of the chance of deformities. It is possible to divide the group into a subgroup with very high resistance and a subgroup with lower resistance, high resistant or typical tuberculoid leprosy and low resistant tuberculoid leprosy.

*High resistant tuberculoid* leprosy presents the typical features of high resistance such as restriction of number and size of lesions, conspicuous asymmetrical distribution, relatively marked hypopigmentation, very sharp definition of the edges, papular surface or central healing with a narrow papular edge, relatively marked hypoaesthesia, loss of hair and loss of perspiration. In a minority of the cases, those who are rapidly selfhealing, the changes in the dermis are minimal and the papular structure is hardly visible. Such patients with one or a few small lesions can be classified as macular tuberculoid. In our experience most macular tuberculoid cases have shown changes in the surface texture and are secondary. The other patients may be divided according to the degree of infiltration and consequently to the degree of elevation into a minor and a major variety.

Typical tuberculoid leprosy is a localised process and most lesions probably indicate the site of inoculation. In a small number of the patients bacilli escape and some secondary skin lesions may be produced. Occasionally a few bacilli reach one or two of the larger nerves. Because of the high tissue resistance such a nerve may be early and seriously damaged, but the nerve involvement is localised (small section of the nerve only) and is as a rule asymmetrically distributed.

The lepromin reaction is strongly positive. Bacilli are not found on routine examination. Relapse seldom if ever occurs.

*Low resistant tuberculoid* leprosy presents predominating tuberculoid features but some of these signs are less marked and they may be even absent in part of the lesions.

The first lesions may be indeterminate or tuberculoid. In the latter case the lesion often is not typical tuberculoid. The whole lesion may be slightly raised, micropapular, only slightly hypopigmented, without much loss of hair, perspiration or sensation and part of the lesion may be



somewhat less well defined. Satellite lesions are common. Some lesions show a weak tendency to central healing but the papular edge remains broad. Sometimes, but not always, a single lesion causes one to suspect low-resistant tuberculoid development, because of the broad edge and the presence of satellite lesions.

Healing of the lesions is slower than in typical tuberculoid patients. In untreated cases more lesions appear, sometimes only one crop, in other cases successive crops.

The number of lesions may be great, but the distribution on the trunk remains asymmetrical. The peripheral parts of the body are usually more effected than the trunk and the lesions show a strong tendency to symmetry. Very often the central part of the face is completely covered with a large lesion or with multiple, coalescing lesions. A butterfly shape on nose and cheeks is often seen. The ear regions are often affected. On the extremities lesions are very often found on both elbows and hands and both knees and feet.

In patients with numerous lesions the lesions on the trunk may also show a tendency to symmetry.

Frequently lesions are found at sites which usually are not affected in typical tuberculoid cases, *e.g.* scalp, ears, nose, chin, palms of hands, soles of feet and genitals.

The larger nerves frequently become involved. Both sides of the body are affected, and in each extremity several or all larger nerves are involved. The nerves are affected over a great length. Consequently the deformity is symmetrically distributed. Although the deformity often develops less acutely than in the typical tuberculoid patients the deformity is often very severe ('beggar-type').

The lepromin reaction is positive but not strongly so. Bacilli may be found in the active stages but are not numerous. They are often found in sections in small numbers in the nerve twigs. Spontaneous arrest is the rule but relapses are not uncommon. Deterioration towards the lepromatous side I have never observed.

Low resistant tuberculoid leprosy logically fits in between typical tuberculoid leprosy and borderline leprosy. The distinction has practical value because of the much more serious prognosis and the need for special precautions in the treatment.

#### *The borderline group*

If the criteria for borderline of the International Congresses are rigidly applied only a very low proportion of the patients can be classified as borderline. If however also patients with multiple macular, maculoid and slightly raised lesions which are not typically tuberculoid, nor typical lepromatous, are included, a logical place for these atypical patients is found. This seems to be permitted as the lepromin reaction in these cases is of the same order as in typical borderline cases and the course of the disease corresponds with the size of the lepromin reaction.

It is not clear which mechanism is responsible for macular, minor, and major tuberculoid lesions. It probably is a factor localised in the skin or a presensitizing factor. It is certain that these are clinical varieties which do not fit into the spectrum of general resistance.

Similarly present classical borderline, with the infiltrated lesions corresponds with a major variety, but for the minor and macular or maculoid varieties no place is reserved in the classification. This has led to the introduction of the controversial use of macular dimorphous, infiltrated dimorphous being similar to classical borderline. In the authors opinion this principle deserves preservation but a more neutral terminology may bridge the gap between difference of opinion.

Some patients, called *borderline tuberculoid*, in which the signs are more at the tuberculoid side, heal spontaneously, although slower than low resistant tuberculoid cases and often only after relapses. They do not become lepromatous. Bacteriology they are more often and longer positive than low resistant tuberculoid patients. Globi are not found. The lepromin reaction is positive but only weakly so, weaker than in low resistant tuberculoid cases. Bacilli often persist in biopsy sections in nerves when the skin lesions have become quiescent and the bacilli have disappeared from the infiltrations.

The nerve involvement is comparable with low resistant tuberculoid leprosy, but in cases without reactions the deformity develops slower and often is less severe. There is little difference in reactive patients.

Borderline tuberculoid leprosy in symptoms and course resembles low resistant tuberculoid leprosy, but evolution and regression are slower. The lesions become more numerous, particularly

on the trunk, and the distribution of lesions is more symmetrical, without becoming completely symmetrical.

Hypopigmentation, loss of hair, of perspiration and of sensation are on the average less marked than in tuberculoid cases. The lesion appear to be somewhat less well defined. Such differences however are more difficult to assess for the less experienced worker than the absence of a papular surface structure and the absence of typical central healing.

The lesions are equally raised throughout the lesion or there may be a tendency to central regression, but complete central healing while the edge is still active is uncommon. In low-resistant tuberculoid leprosy the zone of greatest activity is at the edge, whereas in borderline tuberculoid leprosy the zone of greatest activity is between the centre and the edge. An active lesion may show some depression in the centre and the most infiltrated part slopes away to the edges. This part appears as a hypopigmented halo around the lesion. The slope however is rather steep and visible only after close inspection.

In some cases the first lesion or lesions become "immune areas"

Symptoms and course of *borderline lepromatous* leprosy more resemble lepromatous leprosy, but the lesions appear to be better defined, hypopigmentation is more marked and lasts longer than in lepromatous patients.

The lesions are often dome-shaped, without papular structure, without central healing. The hypopigmented halo is more plainly visible and broader. The slope away at the edges is less steep than in borderline tuberculoid patients. The lesions appear to be less well defined, but the skin in between lesions is normal.

In reactive patients the zone of greatest activity is the most infiltrated central part of the lesion. After reaction the centre may regress more rapidly than the periphery, suggesting central healing. The central healing however is not complete. Immune areas, also those surrounded by fresh infiltration during a phase of reactivity, are more often seen than in borderline tuberculoid patients, but they are present only in a minority of them.

In borderline tuberculoid leprosy it appears that the area is more immune than in borderline lepromatous cases. In the latter not seldom

streaks of fresh infiltration or nodules are seen in the immune area.

The lesions are positive, often strongly so, but large globi are uncommon. The lepromin reaction is doubtful.

The nerves are affected as in borderline tuberculoid, but in patients without reactions the deformity develops slower.

Ups and downs are common, but ultimately the disease is progressive. Although cases may develop far to the lepromatous side, the borderline element can still be recognised in far advanced cases by the definition of the lesions, the presence of hypopigmentation, and the presence of areas of practically normal skin in between extensive infiltration.

#### *The lepromatous group*

Not all lepromatous patients completely lack resistance to *Myco. leprae*. The resistance is shown by a weak response to lepromin, never to a positive degree but still not entirely negligible. There are also clinical signs of resistance corresponding with the size of the lepromin reaction.

In *non diffuse lepromatous* leprosy the disease usually starts with clearly visible hypopigmented macules. They may even last until the disease becomes quiescent. The first macules are indeterminate, but soon the lepromatous classification can be based on the distribution of the macules and the positive smears from both ears. Gradually the macules become infiltrated but the lesions remain somewhat apparent until they coalesce. Nodules may appear in a relatively early stage.

In *diffuse lepromatous* patients the macules are hardly visible and when they are recognised they are already numerous and the distribution is typically lepromatous.

Residual hypopigmentation is not seen. The edges of the infiltration are too vague to be defined. The lepromin reaction is negligible.

#### DISCUSSION

At the uttermost tuberculoid end of the scale a group of 'inoculation lesions' may be recognised. Such lesions appear in individuals with a very high potential resistance to *M. leprae*, who have not yet developed their maximum of effective resistance at the time of infection. In this period they may present papular, papulo-nodules, or lichenoid, small macular lesions or small minor

tuberculoid lesions. Such lesions most likely indicate the site of infection. They heal rapidly and spontaneously. Relapses are not seen, not even after intense and prolonged contact with open cases. The lepromin reaction rapidly becomes strongly positive.

Lara has studied these lesions in detail in young children. The author has found comparable lesions in many adults in New Guinea and Nigeria.

At the uttermost lepromatous end of the scale one could place the *pure, primary diffuse lepromatous* cases, well described from South America but not rare also in other countries. The author has however never seen the Lucio phenomenon in such patients outside South America.

Although nearly the whole skin is affected, there is no visible hypopigmentation nor infiltration. The first visible symptom is a somewhat congested face, more due to edema than to cellular infiltration, and also there may be some loss of eyebrows. Smears are already strongly positive in this stage. Lepromin reaction is virtually nil.

More common are the cases with very diffuse but better visible infiltration. Such cases are classified as diffuse lepromatous leprosy.

Reactional tuberculoid patients are not classified separately. This is a mixed group of patients, some of which are bacteriologically negative or scanty positive, who heal spontaneously after one or two crops of fresh lesions appear (and the lesions are clearly at the tuberculoid side). Such patients are now classified as minor or major low resistant tuberculoid, according to the degree of infiltration. Some patients are less clearly tuberculoid; they may be progressive, presenting several crops of lesions and they are more often positive, sometimes fairly strongly so. These patients are classified as minor or major borderline tuberculoid.

A few patients are progressive, strongly positive and deteriorate towards the lepromatous side. Such patients are included in the borderline lepromatous group.

It is questionable that evolution from major tuberculoid via reactional tuberculoid towards lepromatous really occurs. It seems more likely, that the first major lesion merely was the first stage of a low resistant tuberculoid or a borderline tuberculoid leprosy but that we have failed to recognise the relatively small differences which

cannot always be seen in a single or a few lesions. Particularly in reactive lesions criteria such as degree of hypopigmentation, definition of edges, presence of papules, etc., are difficult to assess.

This concept is supported by the finding that progression was never observed in patients with major tuberculoid like lesions with a strongly positive lepromin reaction but was seen in patients with lesions which looked like tuberculoid lesions but who responded weakly to lepromins. On closer inspection it was often found that the lesions were not as typically tuberculoid as the first impression suggested, but that signs such as satellite lesions, sloping away of edges, hypopigmented halo, surface texture, etc., indicated their true nature.

*Maculo-anaesthetic* leprosy may be divided into a large number of truly benign cases with single or few lesions and a smaller number of more progressive patients, often with serious nerve involvement.

It appears that most benign patients with single or few small lesions can be classified as macular tuberculoid. The fact that the epitheloid foci are minimal and often are found only in serial sections is not a strong argument against a tuberculoid classification. In patients with very few bacilli and a strong resistance to *Mycobacterium leprae* one does not always expect the development of large tuberculoid foci. Also patients are often biopsied after the short stage of greatest activity.

In a minority of the maculo-anaesthetic patients the course of the disease closely resembles low resistant tuberculoid leprosy. The distribution of lesions is similar. The lepromin reaction is weakly positive. Deterioration towards lepromatous is not seen. Such patients are classified as macular low resistant tuberculoid.

*Browne* has mentioned macular patients which are temporarily strong positive, even with globi, and are neither tuberculoid nor lepromatous. I have seen only few cases which correspond with the description. No true globi, but large bunches of bacilli only were found. One wonders if such cases fit into a macular borderline tuberculoid group.

*Dimorphous leprosy* is a hybrid group between tuberculoid and lepromatous, not covered by the term borderline. Some cases are more at the tuberculoid end, others are more at the lepromatous end of the spectrum, some are self healing,

others are progressive. The group comprises cases which are macular, maculoid, and more or less infiltrated. The principle of a larger intermediate group is endorsed. The dimorphous group is subdivided, using a less controversial terminology.

Most if not all dimorphous cases are preceded by an indeterminate stage.

*Polyneuritic* leprosy is not recognised as a separate group or as a subgroup.

It cannot be denied, that primary mononeuritic leprosy may exist, but on the other hand the possibility that the neuritis was preceded by an inoculation lesion, which has healed rapidly and has left a non specific scar only or no residual signs at all, is difficult to exclude.

By chance even a few cases with affection of more than one nerve may occur, but such cases should be rare.

More difficult to evaluate are reports about primary polyneuritic lesions followed by later appearance of skin lesions and deterioration. It is difficult to conceive how a blood or lymph dissemination of bacilli first produces multiple neuritic lesions without skin lesions and that skin lesions are produced after the second dissemination.

One wonders if there had not been vague, selfhealing skin lesions, not noticed by the patient or not connected with the disease which were inconspicuous or not visible any more at the time of examination. This concept is supported by the finding that in many (macular) low-resistant tuberculoid cases and even more in borderline tuberculoid cases the first skin lesions may disappear virtually completely. Often at most some dry patches or a minimal loss of sensation is found and sometimes not even that. The author has found in Nigeria, that in a rather high proportion of patients with polyneuritic lesions who first strongly deny previous skin lesions it is possible to detect traces of former lesions or a history of skin lesions can be obtained. In some cases the skin lesions were not noticed by the patient. It is likely that most polyneuritic cases are secondary polyneuritic.

It is often difficult to distinguish between borderline and low resistant tuberculoid in arrested patients with uncharacteristic residual skin lesions. This could be an argument for a special polyneuritic group or a subgroup of indeterminate leprosy. Here again however the

danger of such a group becoming a 'waste paper basket' for all polyneuritic cases exists. The presence of serious deformity and the absence of visible or anamnestic signs of lepromatous leprosy, points to the tuberculoid side. It is proposed to classify these patients as low resistant tuberculoid, although some may be borderline tuberculoid. This error in classification is not regarded as serious. A more accurate classification is some times possible with the aid of the lepromin test.

One may ask whether a subdivision of borderline and of lepromatous leprosy has any practical significance. In the author's opinion the 'point of no return', regression of progression, is to be found between borderline tuberculoid and borderline lepromatous. It is possible that fluctuations in resistance occur during life, but there is little evidence that such fluctuations are great. Changes, if they occur, are probably limited to the order of one subgroup and only exceptionally go beyond a subgroup.

Secondly, in the borderline tuberculoid group the risk of serious deformity is considerably greater than in the borderline lepromatous group. Only in case of reactions is the nerve damage in the latter early and serious.

Thirdly, the borderline lepromatous patient may resemble lepromatous leprosy. Such patients are unsuitable for drug trials as the response to treatment is much better and even spontaneous remissions occur.

There is some evidence, that the response to treatment of non diffuse lepromatous patients is better on the average than of pure diffuse patients.

On the other hand, the risk of deformity, particularly after reactions is higher in the non-diffuse patients.

Pure diffuse patients, may even after a long, history of the disease and repeated ENL-reactions have good hands and good feet. There seems to be an indication that the incidence of leprosy reactions also is higher in the non-diffuse patients.

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The basis of the classification proposed in this article was used for many years by the author for private purposes and proved to be more satisfactory than international classification.

It was found that other workers (*e.g.*, Ridley and Jopling) independently had thought along the same lines.

Those who have adopted the use of a dimorphous group will have no difficulty in recognising the cases which are not typically tuberculoid, or lepromatous, nor borderline.

The concept of low resistant tuberculoid leprosy was introduced some years ago in the teaching of auxiliary staff in Nigeria and it was found that the difference with typical tuberculoid patients was easily understood.

It is however likely that there will be others who are not ready to accept this subdivision. Also there are several items which need more detailed study. Although every worker, consciously or unconsciously, uses differences in degree of definition, hypopigmentation, etc., on paper it sounds vague. In order to show differences more accurately patients or at least good photographs are needed.

Many fruitless discussions can be avoided if a committee of experienced workers from various countries could study and discuss cases presented with full details. This should include history, follow up, photographic documentation, lepromin test with a single batch of standardised antigen and histopathology, at intervals.

The material should be large and from many endemic areas. It could be supplied by various institutions and studied by the committee. There is no need for the members to come together often but the material could be circulated and discussed mainly by correspondence.

After publication of the results of the study the matter could be more fruitfully discussed in meetings of the International Congresses. This would require a permanent subcommittee for a period of 10 – 15 years at least, who keep touch with the institutions, participating in this study, and to ensure a proper follow up of as many cases as possible.

This time let us seriously attempt to come to an agreement.

#### SUMMARY

The spectral aspect of leprosy is emphasized. Indeterminate leprosy is regarded as a stage in the development towards intermediate forms of the disease. Indeterminate leprosy should not include secondary cases which have shown elevation of lesions, or macular lesions which show tuberculoid features, *e.g.* clearly defined edge and marked hypo-pigmentation.

The tuberculoid group is sub-divided into a

truly benign, high resistant tuberculoid subgroup and a disseminated, more progressive group called low-resistant tuberculoid. The latter often produces very severe deformities. Low-resistant tuberculoid is, as usual, sub-divided into macular, minor and major varieties. Disseminated maculo-anaesthetic lesions fit into the first category. Reactional tuberculoid cases fit into the latter two varieties, according to the degree of infiltration.

The present borderline group comprises only a very small proportion of the intermediate cases. The borderline group is sub-divided into a group of patients with features at the tuberculoid side and a group with features at the lepromatous side. Borderline tuberculoid patients do not deteriorate towards lepromatous, whereas in borderline lepromatous patients the disease is progressive. In order to fit in many patients with intermediate features but without much infiltration, immunologically in the borderline range, maculoid, minor and major varieties are recognized.

Not all lepromatous patients are completely anergic. Many show evidence of a slight tissue defence. The lepromatous group is sub-divided into a non-diffuse and diffuse sub-group.

At the uttermost tuberculoid side of the spectrum a group of 'vaccination lesions' or inoculation lesions, including part of the self-healing childhood lesions (Lara), is recognised. The pure, primary diffuse lepromatous patients (Lucio) are placed at the other end of the spectrum. It is however doubted that special sub-groups are needed for these latter two categories.

This classification scheme reflects the spectrum of leprosy more clearly. The basic, international classification is maintained, the use of controversial terms and of new, unfamiliar designations is avoided. Classification does not become more difficult because the sub-division is based on the degree of tuberculoid and lepromatous, as before. Errors in classification are less essential in a six group classification as compared with a three group classification when they are limited to a shift towards the next group.

The still existing confusion about classification could be materially lessened if leprologists from various countries would be able to study extensive material from many parts of the world. The material should include clinical and anamnestic details, photographs, histology, lepromin reaction

etc., and the patients should be followed up for a period of at least 10 years. The study could be performed mainly by correspondence. The results should be presented for further discussion to the International Congresses of Leprologists.

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# A Preliminary Study of the Absorption, Metabolism and Excretion of Injectable Thiambutosine

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## INTRODUCTION

Oral thiambutosine or 1-(p-dimethylaminophenyl)-3-(p-butoxyphenyl)-2-thiourea, also known as DPT, CIBA 1906 and SU 1906, is extensively used in the treatment of leprosy. Previous studies demonstrated that in man only about 10 per cent of oral doses of thiambutosine of up to 1.5 g are absorbed and that larger doses do not result in increased absorption. Maximum daily absorption (ca. 360 mg) can be achieved by giving 1.5 g thiambutosine thrice daily. After absorption, the butoxy group of thiambutosine is rapidly metabolised and the water-soluble p-dimethylaminodiphenyl thioureas formed are rapidly excreted in the urine. About 75 per cent of the dose is excreted unchanged in the faeces (Ellard, 1961; Ellard and Naylor, 1961).

The possibility of giving thiambutosine by intramuscular injection was therefore investigated with a view to securing complete absorption of the drug. Two preparations of thiambutosine (20 per cent w/v) were supplied by CIBA Ltd., for intramuscular injection. The first consisted of an aqueous suspension and the second was a suspension in arachis oil. The treatment of leprosy with injections of thiambutosine in arachis oil has been described by several workers (Browne, 1965; Dubos and Limbos, 1962; Ross, 1963). The excretion of thiambutosine and its metabolites has been measured in the urine and faeces of patients receiving these two preparations and the previous investigation of the metabolism of oral thiambutosine (Ellard, 1961) was extended to determine whether or not biliary excretion of thiambutosine and its metabolites occurs in man.

## METHODS

Because of the uniform excretion of creatinine in man, the completeness of all 24-hr urine speci-

mens was checked by determining their creatinine content by the method of King and Wootton (1956).

The amounts of thiambutosine and its metabolites (water-soluble p-dimethylaminodiphenyl thioureas) excreted in the urine of patients receiving injectable thiambutosine were measured by two methods:

(a) Half of each 24-hr urine collection was diluted to 1.5 L. Aliquots (100 ml) of diluted urine were then acidified with glacial acetic acid (1 ml) and thiambutosine and its metabolites extracted into benzene/ethyl acetate (1:1) (2 x 10 ml) after the addition of ammonium sulphate (50 g). When the concentration of thiambutosine and its metabolites in the diluted urine was less than 4 µg/ml, 200 ml aliquots of urine were acidified with acetic acid (2 ml) and extracted with 10 ml benzene/ethyl acetate (1:1) after the addition of ammonium sulphate (100 g). Up to 2 ml of the benzene/ethyl acetate extract, containing 10–40 µg p-dimethylaminodiphenyl thioureas, were pipetted into a test tube marked at 10 ml, 6 ml ethanol added and made to the mark with 0.5 per cent acetic acid. After reaction with 0.1 ml 20 per cent (w/v) ferric chloride, the density of the blue colour formed was read within 30 seconds in an 'EEL' colorimeter with a No. 608 or OB1 filter, against a reagent blank of 10 ml 0.5 per cent acetic acid and 0.1 ml ferric chloride. Since the metabolites of thiambutosine do not extract quantitatively into benzene/ethyl acetate (1:1), calibration curves relating the final colorimeter reading to the initial concentration of thiambutosine metabolites were constructed in the following manner:

24-hr blank urines from three patients were pooled and diluted to 9 L. 24-hr thiambutosine-urines from three other patients, who were receiving 1.5 g thiambutosine orally thrice daily,



were pooled and the p-dimethylaminodiphenyl thiourea content determined by reaction with ferric chloride as described previously (Ellard, 1961). The pooled thiambutosine urine, which contained 1.44 g p-dimethylaminodiphenyl thioureas was then diluted to 9 L so that the final concentration of thiambutosine and its metabolites was 160  $\mu\text{g/ml}$ . Aliquots of the diluted thiambutosine-urine and blank urine were then mixed in various proportions to give urine samples containing 1-160  $\mu\text{g/ml}$  p-dimethylaminodiphenyl thioureas. These were then extracted and reacted as described above.

Using this method it was possible to measure a daily excretion in the urine of as little as 3 mg thiambutosine and its metabolites (i.e. a concentration of 1  $\mu\text{g/ml}$  p-dimethylaminodiphenyl thioureas in the diluted 24-hr urine).

(b) When the excretion of thiambutosine and its metabolites exceeded 120 mg/day, the method described previously (Ellard, 1961) was also used. The results obtained by the two methods agreed to within about 10 per cent.

#### Paper chromatography

Descending chromatography on Whatman No. 4 paper was used. In each case 10  $\mu\text{g}$  p-dimethylaminodiphenyl thiourea was applied to the paper.

The solvent systems employed were as follows:

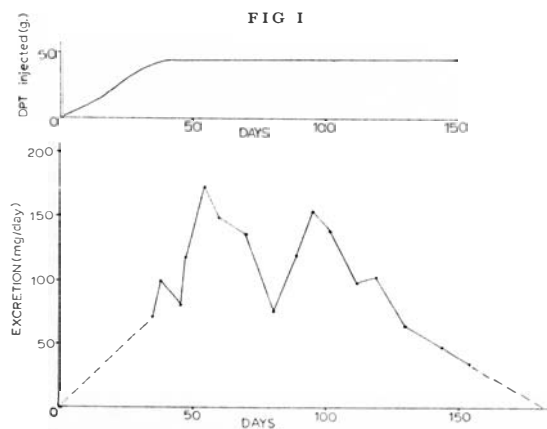
- No. 1 Pyridine/n butanol/ 10 per cent ammonia (2: 1: 1), run for 4 hr.
- No. 2 Ethyl acetate/ benzene/ water (1: 1: 1), run for 2 hr. (Smith and Williams, 1961).
- No. 3 n Butanol/ ethanol/ 3N ammonium carbonate buffer (40: 11: 19), run for 5-6 hr. (Fewster and Hall, 1951).
- No. 4 Benzene/ acetic acid/water (4: 4: 1), run 4 hr (modified from El Masri, Smith and Williams, 1956).
- No. 5 Ammonium acetate buffer pH 4.0 (0.1 M), run for 2 hr.

p-Dimethylamino-diphenyl thioureas were detected on the chromatograms as blue spots by spraying with 10 per cent (w/v) ferric chloride (Smith and Williams, 1961). The detection of the spots was improved by washing the papers with water one minute after spraying with ferric chloride.

## RESULTS

(i) *Excretion of p-dimethylaminodiphenyl thioureas in the urine after intramuscular injection of an aqueous suspension of thiambutosine (20 per cent w/v).*

Four patients were given 23-29 injections of thiambutosine during a period of 30-40 days. The mean excretion of p-dimethylaminodiphenyl thioureas in the urine is shown in Fig. 1 and the results from the individual patients are summarised in Table 1. (N.B.—For convenience 'DPT' is used instead of 'thiambutosine' in the figures and tables).



**Excretion of DPT and its Metabolites after Intramuscular Injection of an Aqueous Suspension of DPT (20% w/v)**

**TABLE I**  
**The Excretion of p-Dimethylaminodiphenyl Thioureas in the Urine after Intramuscular Injection with an Aqueous Suspension of Thiambutosine**

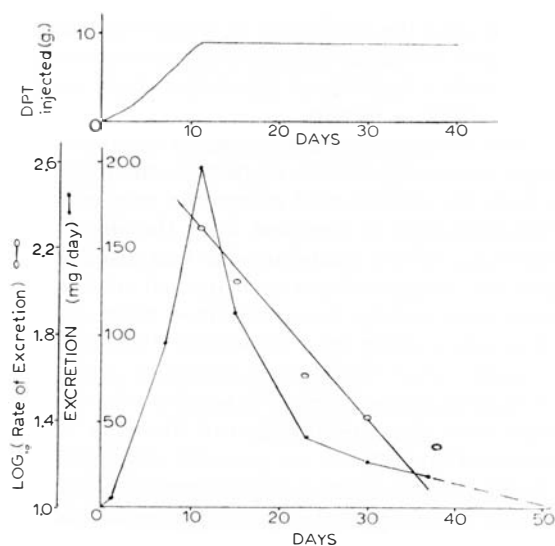
Patient No.	DPT injected g	Total excretion p-dimethylamino-diphenyl thioureas g	% dose recovered
1	39	13.2	34
2	44	17.7	40
3	44	12.1	28
4	51	12.3	24

(ii) *Excretion of p-dimethylaminodiphenyl thioureas in the urine after intramuscular injection of thiambutosine (20 per cent w/v) in arachis oil.*

Six patients were given 7-9 injections of thiambutosine during a period of 9-11 days. The mean excretion of p-dimethylaminodiphenyl thioureas in the urine is shown in Fig. 2 and the results for

the individual patients are summarised in Table 2.

FIG II



**Excretion of DPT and its Metabolites after Intramuscular Injection of DPT in Arachis Oil (20% w/v)**

TABLE II

**The Excretion of p-Dimethylaminodiphenyl Thioureas in the Urine after Intramuscular Injection with a Suspension of Thiambutosine in Arachis Oil**

Patient No.	DPT injected g	Total excretion p-dimethylaminodiphenyl thioureas g	% dose recovered
5	8.4	2.72	32
6	9.6	1.32	14
7	9.6	2.35	25
8	9.6	3.49	36
9	6.8	2.80	41
10	9.6	1.83	19

(iii) *Excretion of thiambutosine and its metabolites in the urine and faeces after repeated oral dosage with thiambutosine.*

Urine was collected for 11 days and faeces for 21 days from a subject who received 1.5 g thiambutosine orally thrice daily for 11 consecutive days. A total of 5.45 g p-dimethylaminodiphenyl thioureas were excreted in the urine (11 per cent of the dose). These compounds were shown by counter-current distribution techniques

to consist almost entirely of water-soluble metabolites of thiambutosine and the least polar metabolite was found to be the 'CIBA Propoxy acid' (Ellard, to be published). This compound is also an important metabolite of the drug in the rabbit (Smith and Williams, 1961). It is obtained by terminal oxidation of the butoxy group of thiambutosine. The amount of thiambutosine excreted unchanged in the urine was estimated at about 45 mg (about 0.1 per cent of the dose).

The faeces were repeatedly extracted with acetone until no more ferric chloride-reacting material could be extracted and the p-dimethylaminodiphenyl thioureas content of the extract determined by reacting with ferric chloride in the presence of 60 per cent ethanol as described in method (a). The excretion of p-dimethylaminodiphenyl thioureas in the faeces, which had ceased completely 10 days after the last dose, totalled 39.9 g or 81 per cent of the dose. Thus in this study it was possible to account for at least 92 per cent of the administered thiambutosine.

Acetone extracts of the faeces were chromatographed in five solvents using thiambutosine, synthetic 'CIBA Propoxy acid' and thiambutosine metabolites (thiambutosine-urine) as markers. The results are summarised in Table 3. In each solvent the ferric chloride-reacting material extracted from the faeces moved as a single spot with an R<sub>f</sub> identical to that of unchanged thiambutosine, and could be distinguished from the 'CIBA propoxy acid' and the other major metabolites of thiambutosine excreted in the urine.

TABLE III

**R<sub>f</sub>-Values of an Extract of Thiambutosine-Faeces and related Compounds**

Solvent	Extract		CIBA	
	DPT	DPT-faeces	DPT-urine	Propoxy acid
1	0.97	0.97	0.80	0.83
2	0.96	0.96	0.91	0.93
3	0.98	0.98	0.47	0.56
4	0.90	0.89	0.37	0.50
5	0	0	0.71	0.71

and slight trail

Other studies showed that the 'CIBA Propoxy acid' has a partition coefficient of  $1.3 \pm 0.2$  in benzene/ pH 4.0 acetate buffer (0.2M) and less than 0.02 in benzene/0.1N NaOH at 25°. Thiambutosine has a partition coefficient of greater than 1,000 in both these solvent systems.

50 ml of an acetone extract of thiambutosine-faeces, containing 420 mg p-dimethylaminodiphenyl thioureas, was evaporated to dryness using a rotary evaporator and the residue extracted with benzene (3 x 20 ml) after the addition of 10 ml pH 4.0 acetate buffer. The p-dimethylaminodiphenyl thioureas were quantitatively extracted into benzene ( $100 \pm 2$  per cent), less than 0.3 per cent remaining in the aqueous phase. On shaking the benzene extract twice with an equal volume of 0.1N NaOH, less than 1 per cent of the p-dimethylaminodiphenyl thioureas were removed. It must therefore be concluded that the ferric chloride-reacting material excreted in the faeces after oral dosage with thiambutosine consists entirely of the unchanged drug.

#### DISCUSSION

It should be emphasized that the results presented in this paper are only preliminary and need confirmation. It should also be noted that the dosage regimens employed in this pharmacological study are very different from those in general clinical use, when weekly or fortnightly injections of 1–2 g of thiambutosine are given in arachis oil.

When thiambutosine was given by intramuscular injection in an aqueous suspension, it was absorbed extremely slowly from the depot (Fig. 1). The daily excretion of thiambutosine and its metabolites in the urine did not reach 100 mg until a total of about 40 g of the drug had been injected. No further thiambutosine was given, but the excretion of thiambutosine and its metabolites continued with little diminution for over two months. It was still possible to demonstrate the excretion of p-dimethylaminodiphenyl thioureas in the urine four months later.

When a suspension of thiambutosine in arachis oil was used for intramuscular injection, the absorption of the drug from the depot was much more rapid (Fig. 2). This is probably due to the greater solubility of thiambutosine in arachis oil than in water. The solubility of thiambutosine in arachis oil at 37° was estimated at about 250 µg/ml and in aqueous acetate and phosphate buffers (pHs 5–7) at about 1.4 µg/ml. After about 10 g thiambutosine had been injected in arachis oil, the daily excretion of p-dimethylaminodiphenyl thioureas in the urine rose to about 200

mg, and in one patient (No. 8) it reached 400 mg. This is similar to the maximum urinary excretion during oral dosage (Ellard, 1961). Injections of thiambutosine were then discontinued and the excretion of p-dimethylaminodiphenyl thioureas decreased almost exponentially, with a half-life of about 6–7 days, to low levels within a month.

The different pharmacological properties of these two preparations emphasise the extent to which the vehicle used affects the rate at which thiambutosine is absorbed from the site of the injection. When thiambutosine was dissolved in polyethyleneglycol-400 and injected subcutaneously into rabbits, it was absorbed more rapidly than when given in a suspension (Schmid and Tripod, 1959). The pharmacological properties of thiambutosine injected in arachis oil may also vary with the concentration of the drug in the preparation, since a 20 per cent suspension of thiambutosine controls experimental tuberculosis in mice more effectively than the same amount of drug injected as a 5 per cent suspension (Kradolpher and Schmid, 1962).

The total excretion of p-dimethylaminodiphenyl thioureas in the urine after injection of thiambutosine never exceeded 41 per cent of the administered dose (Tables 1 and 2). The following possible explanations are considered:

(1) *Biliary excretion of thiambutosine of its metabolites.*

Schmid and Tripod (1959) have shown that when thiambutosine is injected intravenously into the rabbit, the drug or its metabolites are excreted in the bile and through the intestinal wall. However when thiambutosine was given subcutaneously, dissolved in polyethyleneglycol-400 or as a suspension, measurable concentrations of the drug or its metabolites could not be detected in the faeces.

A 24-hr collection of faeces was made from one of the patients receiving the aqueous suspension of thiambutosine by intramuscular injection, who was excreting over 100 mg p-dimethylaminodiphenyl thioureas in the urine each day. Less than 2 mg p-dimethylaminodiphenyl thioureas could be detected in the faeces. If biliary excretion of thiambutosine or its metabolites had been responsible for the discrepancy between the amount of thiambutosine injected and the p-dimethylaminodiphenyl thioureas excreted in the urine, the biliary excretion of thiambutosine and

its metabolites would have averaged over 170 mg/day during the whole six months period.

Williams, Millburn and Smith (1965) studied the biliary excretion of a number of foreign compounds in the rat and showed that the compounds excreted to the greatest extent in the bile were polar conjugates of large molecules. Thiambutosine was not excreted unchanged in the bile but as two metabolites which appeared to be glucuronides. Since over 99 per cent of the p-dimethylaminodiphenyl thioureas excreted in the urine of patients receiving oral thiambutosine consist of water-soluble metabolites of the drug, it might be anticipated that biliary excretion would lead to the elimination of metabolites of thiambutosine in the faeces. The fact that no such metabolites could be demonstrated in the faeces after oral dosage with thiambutosine strengthens the conclusion that biliary excretion of thiambutosine and its metabolites is of no importance in man. It is possible however that small amounts of thiambutosine metabolites are excreted in the bile and then quantitatively reabsorbed from the gut.

Emerson and Nicholson (1965) have studied the absorption of orally administered p, p'-diisomyloxydiphenyl thiourea (Isoxyl) in man using  $^{35}\text{S}$ -labelled drug. At a dose of 6 g/day, in divided doses, the absorption of this diphenyl thiourea is also very limited. Less than 2 per cent of the dose was excreted in the urine and less than 0.2 per cent in the bile.

(2) *Metabolism of thiambutosine to compounds not estimated by ferric chloride.*

When thiambutosine is given orally, all the metabolites of the drug can be estimated by reaction with ferric chloride (Ellard and Naylor, 1961). Although the metabolic fate of compounds in the body is usually relatively unaffected by the amount of drug metabolised, it is possible that when small amounts of thiambutosine are continuously absorbed from the site of injection, a significant proportion of the drug may be metabolised to compounds that could not be determined by the methods employed in these studies. Such a possibility can only be answered by using isotopically labelled thiambusotine.

(3) *Incomplete absorption of thiambusotine from the site of injection.*

Owing to the extremely low solubility of thiambusotine in water (about  $1.4 \mu\text{g/ml}$  at pHs 5–7 and  $37^\circ$ ) it is possible that a considerable

proportion of the thiambutosine deposited at the site of injection remains unabsorbed. There is some evidence from animal experiments supporting this possibility. Schmid and Tripod (1959) injected rabbits subcutaneously with thiambutosine, dissolved in polyethyleneglycol-400 or as a suspension. Under these conditions the drug was incompletely absorbed. After six days only about 21 per cent (solution) and 7 per cent (suspension), respectively, of the dose was excreted in the urine and some of the drug still persisted at the site of injection (percentages excreted calculated from Fig. 6 of Schmid and Tripod, 1959). In the mouse 6 per cent of the drug could be recovered from the site of injection 20 days after subcutaneous dosage (Kradolpher and Schmid, 1962). It should be possible to make a direct study of the extent and rapidity of the absorption of injectable thiambutosine in man by measuring the concentrations of thiambutosine in biopsies taken from the site of injection after various time intervals.

#### SUMMARY

1. An aqueous suspension of injectable thiambutosine was absorbed extremely slowly and metabolites of thiambutosine could be demonstrated in the urine four months after injections of the drug had been discontinued.
2. Absorption was accelerated when thiambutosine was injected in arachis oil, its half-life in the body being reduced to about 6–7 days.
3. The total excretion of thiambutosine and its metabolites never exceeded 41 per cent of the injected dose and it is possible that the drug was incompletely absorbed from the site of injection.
4. Thiambutosine or its metabolites could not be detected in the faeces in significant amounts after intramuscular injection of the drug, and it was concluded that biliary excretion of these compounds is not important in man.

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# Some Observations on the Morphological Index in Lepromatous Leprosy

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The Morphological Index (M.I.) may be defined as the average of the percentages of morphologically normal forms ('solid rods') of *Myc. leprae* found in smears taken from a given number of sites by a standard procedure and stained and examined by a standard technique. It thus indicates the proportion of bacilli that are presumably viable and capable of multiplying. There is the same need for uniformity in obtaining and expressing the M.I. as there is for the Bacterial Index (B.I.) if results from one centre and another, from different patients at the same centre, and from the same patient on different occasions are to be comparable. Technique, and the criteria for dividing the stained bacilli into 'solid rods' and 'other forms', are standardized. These 'other forms' comprise coccoid and irregularly stained organisms, acid-fast debris having the general outline of bacilli, and acid-fast dust no longer recognizably bacillary in form. This second morphologically heterogeneous group thus includes all varieties of degenerate and effete bacilli, presumably non-viable and incapable of multiplying.

The M.I. probably furnishes the most direct and delicate indication available of the efficacy of a bactericidal or bacteriostatic drug; it is an index of a comparatively simple therapeutic effect, uncomplicated by such factors as removal of non-viable mycobacteria and immunological response to antigenic acid-fast material.

Two aspects of drug therapy needing emphasis concern the wide range of variation existing between one untreated patient and another in the proportion of bacilli morphologically normal, and the variation of this proportion in the natural history of the untreated disease. While it is not nowadays ethically justifiable to deny treatment to an individual patient, it so happens that opportunities occur from time to time to observe these changes.

Failure to recognize these variations may vitiate the results deduced from therapeutic trials. Their importance underlines the difficulty of 'pairing' in double-blind trials by adding an important but unpredictable variable to the number of primary considerations already to be appraised – age, sex, form of leprosy, its severity and duration, the B.I., etc. The inherent difficulties of observation and interpretation of the results of a prolonged therapeutic trial in which both bacterial morphology and tissue reactivity are assessed, are thus aggravated by the virtual impossibility of beginning the trial in the same circumstances with an adequate number of comparable individuals.

The present paper summarises an analysis of the M.I. findings in 154 patients with lepromatous leprosy recently under observation in the Research Unit, Uzuakoli.

## *Technique*

Material from eight sites (two each from the edge of a lesion, from the ear-lobes, from apparently normal skin, and from the nasal mucosa) is taken every fortnight for two months, and then at monthly intervals until individual bacilli are no longer recognizable.

The percentage of normal forms is estimated from examination of 200 bacilli from typical fields, excluding globi, since it is impossible to determine the form of the individual bacilli present in globi.

## *Initial height of the morphological index*

Every care was taken to ascertain that these patients had never taken anti-leprosy drugs obtained clandestinely. The serum of several patients selected at random was examined by the Bratten and Marshall technique for the presence of sulphones, and found to be negative.

The B.I. was calculated on the Dharmendra notation, in which the range is zero to 4.0.

The initial height of the M.I. in the untreated patient with lepromatous leprosy, completely Mitsuda negative, was found to vary within the widest possible limits. In nine patients, over 94

per cent of bacilli were classified as morphologically normal, whereas in five, fewer than 10 per cent could be called normal. In two of the first group, all the bacilli were normal, and in one of the latter, none were normal.

The range and scatter are summarized in:

TABLE I

Number of patients	B.I. range	Average	M.I.				Average per cent morpho- logically normal forms
			75—100 per cent	50—74 per cent	25—49 per cent	0—24 per cent	
88	3.0—4.0	3.39	26	39	14	9	51
53	2.0—2.9	2.50	12	19	16	6	41
13	1.0—1.9	1.66	5	1	2	5	41

Just as the B.I. is the average of the Index from all the sites smeared, the M.I. similarly takes no cognizance of variations between the sites, since for the general purposes for which the indexes are employed, such distinctions are not important. It is, however, worthy of note that the M.I. may show considerable differences between the different sites smeared; in particular, smears from the nasal mucosa often reveal a much higher index than those from skin and ear-lobes, the higher index may persist for longer in the nasal mucosa, and normal bacilli may reappear in the nasal mucosa but not elsewhere.

The initial height of the M.I. is not related directly to the height of the B.I. The number of normal *Myc. leprae* appearing, and subsequently sampled by the slit-scrape technique, is a factor of the slow generation time of the bacillus. In the natural state, the number degenerating and losing their viability depends partly on a built-in survival time and partly on inimical factors in the micro-environment. The proportion of 'solid rods' and 'other forms' is the result not only of the combined effects of these factors, but also of the speed of removal from the tissues of non-viable and, possibly, also of viable bacilli. The absolute and relative importance of these various factors is still obscure and demands further investigation.

In general, and confirming clinical observations, the density of *Myc. leprae* and of globi per unit volume of tissue, as shown by the ordinary techniques of examination, increases with the duration of progressive lepromatous disease, but

the height of the M.I. bears no direct relation to the actual volume of the granuloma that is sampled by smearing.

#### *The rate of decrease in the Morphological Index*

The speed at which the proportion of 'solid rods' progressively declines in the smears taken from the different sites in skin and nasal mucosa is commonly taken as the best evidence available for the efficacy of the drug under investigation. The component due to the action of the drug in the rate of decrease in the M.I. may, however, be supplemented both by the above-mentioned suspected factors causing variation in the height of the M.I., and by possible strain differences of *Myc. leprae* (as in *Myc. tuberculosis*).

It was found that in lepromatous leprosy with no borderline features the rate of fall in the M.I. bore no relation to its initial height. Patients with a low M.I. (of 10 to 30, for instance) might continue to harbour normal bacilli for twelve months or more, whereas those with a M.I. of 85 or over might cease to have normal bacilli in their smears within three months of the beginning of treatment.

As far as possible, by clinical assessment, and by the lepromin test, care was taken to exclude from this series any patient presenting borderline features, which are known to be associated with rapid fall in the M.I.

There was, however, some relation between the rate of fall of the M.I. and the initial height of the B.I., as shown in:

TABLE II

<i>B.I. range</i>	<i>No. of patients</i>	<i>Persistence (in months) of normal bacilli in smears</i>				<i>Average (months)</i>
		0-5	6-10	11-20	over 20	
3.0-4.0	88	16	35	28	9	11.3
2.0-2.9	53	15	29	5	4	8.1
1.0-1.9	13	5	1	2	5	5.8

It is evident that the fall in M.I. in patients under treatment will depend on the properties of the drug, the total bacterial population, and the accessibility of this population to effective concentrations of the drug. The known efficacy of widely-spaced small oral doses of dapsone is probably explicable on the basis of the long generation time of *Myc. leprae*. The actual level of sulphone present in the serum at a given moment bears no necessary relation to any essential aspect of therapeutic activity. The extreme infrequency of true resistance to dapsone would support this supposition.

*The rate of decrease in the Morphological Index and its relation to the disappearance of all acid-fast debris*

It was found that there was no relation between either the initial height of the M.I. or its rate of fall, and the time taken for the clearance of all acid-fast debris from the sites smeared. Granted that a considerable concentration of normal bacilli must be present for a few to be seen in an ordinary microscopic smear preparation, it is nevertheless probable that repeated careful smearing which reveals consistent reduction in the loads of acid-fast debris would reveal now and again 'solid rods' if they were present in appreciable numbers.

It is customary to continue anti-leprosy treatment in patients with lepromatous leprosy for at least two years after the disappearance of acid-fast material from all the smears. This course, and its corollary 'treatment for life at half the therapeutic dose', may in the present state of knowledge be advisable in view of the possible persistence of viable *Myc. leprae* between nerve fibres

and in deep organs, but it may be an unnecessary counsel of perfection in the majority of patients.

*Variation in the rate of fall of the Morphological Index in relation to the drug administered*

In view of the considerations detailed above, it is not expected in such small series that there would be any clear-cut difference in the rate of fall of the M.I. depending on which of the recognized effective drugs were taken. The scatter was not greatly different as between dapsone (in standard or in small doses) and thiambutosine. B663 showed a definite slight superiority.

It was observed that whatever the drug given, a small proportion of patients (about one in eight) appeared to respond very slowly as judged by the rate of fall of the M.I. In about three-quarters of patients with lepromatous leprosy in this series, 'solid rods' disappeared well within fifteen months; in the remaining quarter, they persisted for longer, in some cases for much longer. This observation, if confirmed in larger series, might suggest the possibility of a genetically determined difference in inactivating the drugs used, like the INAH-inactivation shown in some patients under treatment for tuberculosis (Mitchison, 1965).

#### SUMMARY

The Morphological Index (which is an expression of the average proportion of 'solid rods' found in multiple smears), has a considerable range in the untreated patient with lepromatous leprosy.

The M.I. bears no relation to the height of the Bacterial Index, nor necessarily to the rate of fall of that Index in the individual patient, nor to the time taken for all acid-fast material to disappear from the skin and nasal mucosa.

A small number of patients appeared to respond slowly, as judged by the rate of fall of the M.I., to standard therapeutic regimes.

#### ACKNOWLEDGEMENTS

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# Low Dosage of DDS

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Preliminary report on progress of lepromatous patients on low and high dosages.

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The maximum dosage of DDS in leprosy clinics in Northern Nigeria supervised by Government was 600 mg, once weekly. Recently the maximum dosage was reduced to 400 mg weekly. In some clinics supervised by voluntary agencies the maximum dosage was 800 mg DDS weekly. At present in most clinics the Government scheme is adopted. The general impression was that the incidence of reactions was higher in clinics with a high dosage scheme, and that progress of the patients was not better than in Government clinics.

In many Government clinics on the average 50 – 60 per cent of the patients attend very regularly. Such patients receive an average weekly dosage of 500 – 600 mg DDS. About 20 per cent of the patients attend less regularly, but still fairly regularly, and they receive not more than an average dosage of 200 – 400 mg DDS weekly. The bacteriological status of several hundred lepromatous patients who had been on treatment for several years was compared. It was found that the bacteriological index did not differ greatly in very regularly attending and fairly regularly attending patients after a comparable number of years of treatment. The bacteriological index was however significantly higher in those who had attended very irregularly. These findings suggested the possibility that a lower dosage of DDS might be as effective as a higher dosage. Therefore a limited pilot trial was initiated in the Bornu Provincial Leprosy Settlement at Molai.

A number of lepromatous cases with a high bacteriological index was selected. The patients were examined by the first two authors. Borderline cases and borderline lepromatous cases were excluded from the trial. The register numbers of

the patients were written on pieces of paper. The papers were thoroughly mixed and thereafter the first number that was drawn, was put in group 1, for 200 mg DDS weekly, the second number in group 2 for 400 mg DDS weekly and the third number in group 3 for 800 mg DDS weekly, etc. Six smears were taken monthly. The average bacteriological index of the smears of two months are given in table I.

At the beginning of the trial, and furthermore every three months a punch biopsy specimen was taken from one lesion, the next one as near as possible to the previous one. The biopsies were kept until the end of the trial and then processed in one period in order to avoid differences in staining technique as much as possible.

Assessment was made by counting bacilli (bacillary index), by counting the percentage of intact bacilli and by measuring the percentage of the section affected by infiltration. The examiner did not know the patient whose sections were examined, nor the group to which the patient belonged. These three data are also given in table I.

In group 1 and 3 a number of patients reacted repeatedly and severely. Such patients have received much less than the scheduled dosage. The groups therefore were subdivided into a group of patients who had no reactions or only one or two reactions and a group of patients with four or more reactions.

Between the group of patients on 200 mg and those on 800 mg, who had only few reactions, no marked difference in decrease of bacillary index was found. The decrease in percentage of intact bacilli was more marked in the 200 mg group. The decrease in percentage of the sections that is affected by infiltration is of the same order.

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TABLE I

**Group I – 200 m. DDS**

<i>Bacteriological Reg. Nr. Index Biopsy</i>											<i>Bacteriological Index Smears</i>					<i>Percentage of Intact Bacilli</i>					<i>Percentage of section with infiltration</i>					<i>Number of reactions</i>	
1947	5	5	5	5	1	5.0	5.0	2.5	1.3	0.8	6.8	6.2	3.6	5.0	0.1	27	30	3	8	—	0						
1957	5	5	5	5	—	4.5	2.0	3.2	2.7	—	15.9	3.9	3.8	0.5	—	21	30	35	18	—	0						
1968	5	5	4	4	4	5.0	3.3	3.0	3.2	—	3.8	5.3	7.3	6.5	4.0	41	60	40	33	3	0						
1979	5	5	5	4	1	3.5	3.5	2.4	1.4	.12	18.0	13.0	8.0	7.5	1.6	64	21	60	36	30	0						
1904	4	5	4	4	1	3.0	3.0	3.5	3.8	3.5	6.3	1.2	6.2	0.5	0.1	30	40	22	42	12	0						
1989	5	5	4	5	—	6.0	4.3	2.4	2.7	0.5	5.1	7.3	5.4	8.0	2.5	5	15	4	19	—	2						
<i>Average</i>	4.8	5.0	4.5	4.5	1.2	4.5	3.5	2.8	2.5	1.0	9.3	6.0	5.7	4.7	1.7	32	32	32	25	13	0.3						
1941	5	5	—	4	4	4.0	3.8	4.3	3.6	3.5	1.7	10.1	—	0.5	3.9	25	21	—	14	12	5						
1948	5	5	—	5	5	1.0	—	3.0	3.7	2.7	0.7	0.1	—	10.0	38.0	36	11	—	20	4	5						
1936	5	5	5	4	1	3.0	3.5	3.4	3.1	2.8	0.8	0.1	2.1	1.0	3.5	45	33	76	60	20	9						
1938	5	5	—	5	1	4.0	3.0	3.7	3.8	3.0	0.7	3.5	—	0.1	0.1	6	12	—	8	2	9						
<i>Average</i>	5.0	5.0	5.0	4.5	2.3	3.3	3.4	4.8	4.7	4.0	1.0	3.5	2.1	2.9	11.5	28	19	—	25.5	9.5	7.0						

**Group II – 400 mg. DDS**

1962	5	5	5	3	—	4.0	3.0	2.7	4.3	1.3	2.8	0.1	3.4	0.1	—	75	30	32	63	—	0					
1950	5	5	5	5	5	1.5	1.0	1.8	1.3	1.0	2.5	5.0	5.3	1.2	1.3	3	3	5	7	4	0					
1923	5	—	4	4	4	0.5	1.3	0.9	2.3	0.7	1.3	—	1.8	2.0	1.5	2	—	15	20	3	0					
1118	5	6	5	5	—	4.0	3.0	5.2	5.1	4.0	0.9	4.8	1.5	0.3	—	77	70	48	18	—	0					
1951	3	3	2	3	1	1.5	2.8	2.5	0.3	0.3	1.0	1.0	2.3	1.0	0.1	40	70	15	33	34	0					
1770	4	4	4	4	—	1.5	1.5	1.0	1.0	—	0.1	4.0	6.2	3.0	—	3	22	5	8	—	2					
<i>Average</i>	4.5	4.7	4.1	4.0	3.3	2.2	2.1	2.4	2.4	1.5	1.4	3.0	3.4	1.3	1.0	33	36	31	24	21	0.3					

**Group III – 800 mg. DDS**

1954	5	5	5	5	5	2.5	2.0	2.0	2.9	—	0.7	7.2	4.9	4.0	6.4	15	28	20	15	28	0					
1914	5	5	5	5	4	1.0	1.0	1.0	0.7	0.8	1.6	3.4	3.3	6.1	4.1	3	27	25	9	7	0					
1956	5	5	4	—	4	4.5	3.8	2.9	3.3	2.7	11.6	9.0	1.6	—	8.3	79	32	35	38	14	0					
1543	5	5	—	5	5	5.0	5.0	1.2	2.2	0.8	5.0	7.2	—	4.0	5.0	35	58	—	42	35	0					
1673	5	5	5	5	—	2.0	1.5	1.7	2.2	—	1.4	3.4	4.7	4.6	—	6	3	16	18	—	1					
1924	5	5	4	4	1	3.5	3.5	2.4	3.3	3.2	0.8	1.6	4.9	0.9	1.5	65	30	7	15	7	1					
1925	5	5	5	1	—	4.5	2.5	0.6	1.7	1.5	1.6	4.4	1.0	6.3	—	4	25	9	4	—	2					
<i>Average</i>	5.0	5.0	4.7	4.3	3.8	3.3	2.8	1.7	2.3	1.8	3.2	5.2	5.7	4.3	5.1	30	29	19	20	18	0.6					
1902	4	4	4	4	4	1.3	0.8	1.6	1.4	0.7	0.9	1.5	4.3	3.2	2.8	14	52	11	42	25	4					
1945	5	5	—	5	4	3.5	1.5	3.5	4.7	2.5	1.0	2.0	—	0.2	0.5	37	5	—	11	45	5					
1952	5	5	5	5	5	6.0	4.5	4.8	4.3	4.7	6.8	5.9	4.8	2.0	3.9	35	35	20	16	9	7					
<i>Average</i>	4.4	4.4	4.5	4.4	4.3	3.9	2.3	3.3	3.5	2.6	2.9	3.1	4.5	1.8	2.4	29	31	16	23	26	5.3					

Progress was in all aspects less good in the group of patients with repeated reactions, despite the much lower dosage received by these patients.

From this limited trial it seems that the lower dosage of 200 mg DDS weekly is not less effective and may even be on the average more effective than the higher dosages. The method of assessment in this trial is regarded as more reliable than the usual method of evaluation of smears only. However, because of the limited number of patients on trial, no final conclusions are drawn,

but the trial will be continued with a large group of patients on less than 100 mg and 600 mg DDS respectively, for a longer period.

#### SUMMARY

The assessment of biopsies and smears from a series of lepromatous patients on treatment with 200 mg, 400 mg and 800 mg DDS once weekly, strongly suggests that the lower dosage is on the average at least as effective, as the higher dosage. A larger trial series is needed for conclusive evidence.



# A Study of Spontaneous Sweating of Ring and Little Fingers in Leprosy

## (A Preliminary Communication)

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The volar surface of human hands sweats spontaneously and perpetually. The sweating rate is under the control of autonomic nerves and is considered a fairly reliable indicator of the ability of the human volar sweat glands to respond to sudorific stimuli if the sweat glands are normal. Therefore it can be usefully employed in the assessment of extent of involvement of autonomic innervation of the part supplied. The sweating rate can be easily measured simply by counting the number of sweat spots.

Anidrosis is a common feature of leprosy. Disturbances in sweating in leprosy are attributed to affection of the sudorific nerves and the sweat glands themselves. The ulnar (a mixed nerve) is frequently affected in the disease, producing alterations, both in the somatic and autonomic activity in the area supplied. Consequently changes are noted in the sweating rate of the ring and little fingers and the hypothenar eminences of the hands.

Any test employed in leprosy work should be such that it could be easily performed in the field by paramedical personnel, without much instrumentation. It should be quantitative, simple and not very time-consuming; so that the patients would easily return for re-examination from time to time. With these objectives in mind the Wada<sup>2</sup> (1948) test for detection of secretion of sweat as modified by Silver A<sup>1</sup> (1963) was employed in this study of secretory activity of the volar sweat glands of ring or little fingers of subjects who have leprosy.

## METHOD

The area under study was clean dried with absolute alcohol. A circular area was marked on the volar aspects of the terminal phalanges of ring and little fingers. A cap of a thermometer cover was used to mark a circle. It encircled an area of 150 square mm. The sweat pores were counted by

using a magnifying lens with a built-in illuminating bulb of a dry cell torch. It is necessary to test identical contra-lateral sites as well as the identical areas in different subjects to reduce the effect of such factors as variation in the population density of sweat glands, the number of nerve endings, and callosities etc. The counting was done 15 minutes after the application of iodine and a thin layer of starch on to the area under examination. Under this magnification they appeared as circular black spots arranged along the epidermal ridges.

## MATERIAL

In this work, we have studied hands of healthy subjects (Group A) along with those of patients subject to leprosy without any obvious deformity due to involvement of the motor element of the ulnar nerve (Group B) and hands in leprosy patients with obvious deformities (Group C) due to affection of the motor component of the ulnar nerve irrespective of the type of disease. In these patients we recorded the type of leprosy along with other relevant clinical data.

Readings were taken in each case on three successive days during the same hours of the day (8.00 a.m. to 9.30 a.m.) in a quiet room. To avoid excitement the patients were made to lie comfortably for 30 minutes in the experimentation room prior to taking actual readings. All the readings of all the patients were made in the lying down position. As there was no significant variability within the set of the three readings taken on successive days in any of the cases (statistically tested), a mean of the three readings was used in all the cases for further calculations.

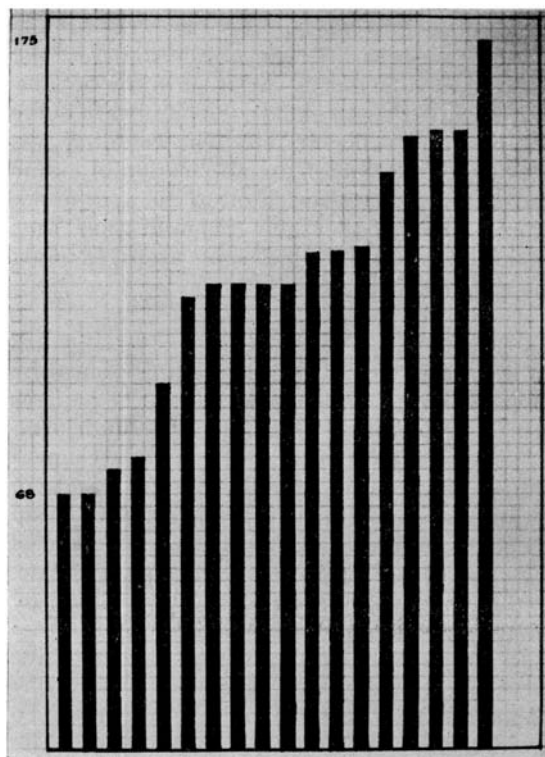
Some subjects were studied every month all round the year to observe any seasonal variations in sweating rate.

The study of healthy hands all round the year indicates that there are no significant variations

in the sweating rate under the ordinary conditions of seasonal changes of temperature and humidity. It has become apparent that relatively extreme thermal stimuli are required to activate simultaneously one and all the functional sweat glands in any given area.

#### RESULTS

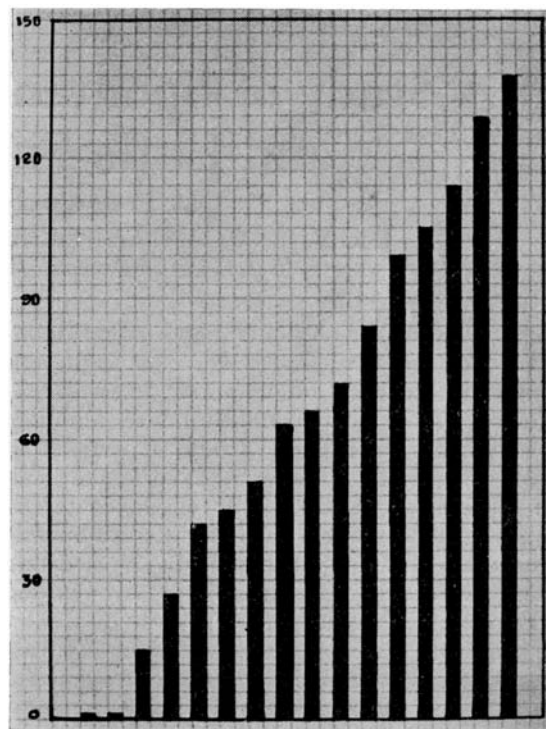
As it was statistically found out that the groups A, B and C differed from each other in respect of their readings (Analysis of variants table was used) the results have been recorded as follows:



(GROUP A)

Number of perspiring pores of healthy hands

The study of healthy hands (group A) shows that there are no significant variations in the sweating rate between the right and left hands. There is not a single case of zero reading. The ring finger has a larger number of sweating pores than the little finger. It is known that different fingers have characteristically different sweating capacities and that the ring finger is usually the most active one.

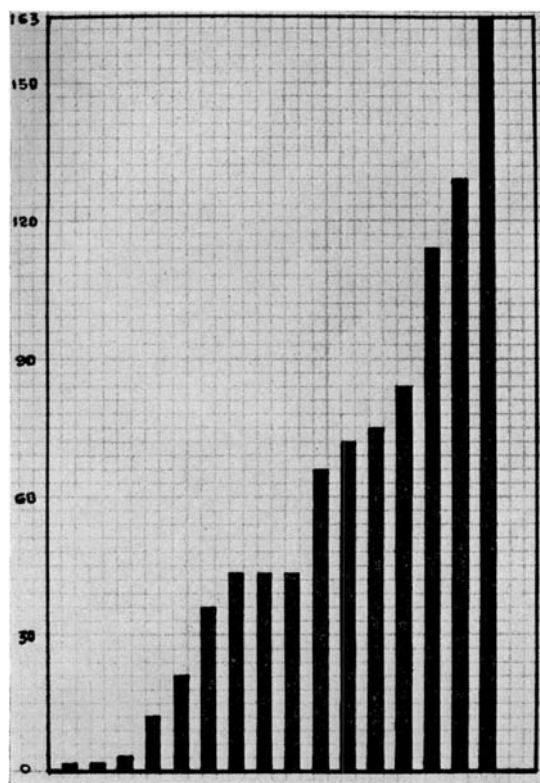


(GROUP B)

Number of perspiring pores of undeformed leprosy hands

When the sweating rate of ring and little fingers of healthy hands is compared with those of undeformed hands of leprosy patients (group B) it is observed that there is a statistically significant fall in the number of sweating pores of the fingers of leprosy patients even after excluding extreme cases of zero readings. The same pattern is observed when the healthy hands (group A) are compared with leprosy hands with obvious deformities (group C). Histograms 1, 2 and 3 represent the readings of group A, B and C. The sweating rate of fingers of the right and left hands of leprosy patients of group B do not show any statistical difference. However in the case of group C though the value of T of sweating pores between the two hands is not significant; yet the value of T is not very negligible. The number of sweating pores in the affected hands is less.

In the group B there are two cases in which both the fingers of one of the hands do not perspire at all. Both these two cases belong to maculo-anaesthetic type of leprosy. In two other



(GROUP C)

Number of perspiring pores of deformed leprosy hands

cases only little fingers are affected. One of these cases is a case of maculo-anaesthetic type and the other is of lepromatous variety. In the group C (deformed hands) there are two cases where both the little and ring fingers of one of the hands does not show any perspiring pores. Both these hands are deformed while their counterparts are not deformed. These cases are of lepromatous type. There are five patients with zero reading of little fingers only. In this group, there is one patient each of maculo-anaesthetic neural and lepromatous types. The remaining two cases are of tuberculoid type.

#### OBSERVATIONS

From the present study it can be surmised that the number of sweating pores on the volar aspect of ring and little fingers of leprosy hands is lesser than the normal hands. The deformities consequent on motor nerve involvement do not seem to have close co-relationship with the perspiring pores. On calculation of standard deviation it has been found out that the scattering is less in healthy hands as compared with the leprosy hands. The scattering in deformed hands of leprosy patients is more than undeformed leprosy hands.

Further studies to evaluate the individual part played by the autonomic element and the sweat glands themselves in the fall of rate of sweating pores in leprosy is under way.

#### SUMMARY

The sweating rate of the volar aspects of ring and little fingers of healthy and leprosy subjects is studied.

It is observed that there is a significant fall in the number of sweating pores in leprosy.

#### ACKNOWLEDGEMENTS

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# Reconstructive Surgery in the Treatment and Prevention of Ulcers of the Foot

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This article is based on the paper read at the seventh all India Leprologist's Conference held at Bombay in December, 1959.

Not enough attention is given to the various mechanical factors in the ulceration and absorption of the foot. Much has been said about the medical treatment of ulcers. The literature on this subject is enormous. A great variety of local applications, local injections and systemic medications have been tried. When these are combined with rest and care they all succeed. When used without these precautions the ulcers either fail to heal or recur when they have healed.

The chief aim in presenting this paper is to stress the importance of understanding the various mechanical factors that cause ulceration and absorption of the feet.

In leprosy this depends on the understanding of the distinction between the trophic changes and the mechanical factors in the causation of various deformities, particularly the ulceration of the feet and the absorption of bones. It is universally agreed that there is trophic change in the denervated tissues and these tissues are less able to bear the normal physiological strains than normal tissues. Unfortunately, this trophic change is not ordinarily reversible. Lumbar sympathectomies were done to produce vasodilatation in the limbs to increase the blood supply. Gokhale and Watt Maney *et al.* have used Hydergin and its alkaloids to produce vasodilatation in the limbs, but we know that the anaesthetic foot is already fully vasodilated because of the destruction of the sympathetic nerve fibres produced by the leprosy neuritis. It is important to differentiate between the arterial changes that lead to ulceration and arterial changes that result from ulceration leading to scarring. In leprosy, the limitation of blood supply to an ulcer in the foot is not due to vasoconstriction but is due to strangulation of vessels by a mass of non elastic fibrous tissue. This is un-

affected by medication either external or internal. It is due to previous ulceration.

Brand emphasised in many of his articles and lectures the doctrine of the first ulcer. The patient's first ulcer is usually due to an excessive amount of walking, a badly fitting shoe, or some trivial injury. When proper care is taken by giving complete rest to the foot it heals; but as it heals it creates fibrous tissue. His second ulcer will be due to the fibrous tissue of his first ulcer plus a smaller amount of trauma. His fifteenth ulcer will be due to his previous fourteen ulcers and an almost negligible amount of trauma.

Hospitalisation and education of all patients with the first ulcer will reduce the recurrence of ulcers to a great extent. There are a number of difficulties in getting the patient with the first ulcer into the hospital. Quite a large percentage of our patients do not pay as much attention as they should to the ulcers on their feet because the pain that drives them to the hospital is not there. The accommodation and care of these patients who obviously are not very sick is woefully inadequate. It is essential to explain to the patient at this stage about his first ulcer and how necessary it is to replan his mode of life. With a few restrictions such as wearing well fitted shoes or changing the place of work or residence avoiding walking long distances, the patient may lead a useful life of reasonable activity.

Some of the mechanical factors which are responsible for the production of ulcers are:

- 1.—Excessive amount of walking.
- 2.—Injuries caused by sharp stones, thorns and nails in the shoes.
- 3.—Type of weight bearing. Normally, the weight of the body is transmitted to the ground through a pad of elastic fibro-fatty substance. This distributes the strain of weight bearing to a large area of skin. After each ulceration, this

elastic fibro-fatty substance is replaced by non-elastic scar tissue which transmits the weight bearing through a very small area of skin thus increasing the danger of recurrence. A vicious circle is created whereby ulcers create fibrous scar tissue which in its turn predisposes to further ulceration.

4.—The concentration of weight at certain points of the foot. The common pressure points are (a) Under the metatarsal heads, (b) the lateral side of the sole of the foot, (c) the heel, and (d) the tips of the toes.

5.—The projection of bone downwards towards the sole of the foot encouraging localised pressure. Ulceration and sepsis loosens the attachments of metatarsal heads and allows them to project into the ulcer. This bone delays the healing and causes recurrence not by its diseased nature but because of its position just under the skin. In claw toes there is hyper-extension at the proximal segment and acute flexion at the distal segment which leave the metatarsal heads uncovered thus exposing them to more pressure and trauma. The acute flexion at the distal segments of the toes also predisposes to ulceration of the tips of the toes.

6.—Drop foot and inversion caused by paralysis. These factors cause uneven distribution of the weight. The drop foot causes dragging resulting in ulceration. The inversion causes ulceration on the lateral side of the sole of the foot.

It is to be emphasised that by treating all these factors simultaneously one can reduce the incidence of ulceration.

Let me take a single mechanical factor—drop foot and inversion caused by paralysis. Drop foot can be corrected three or four ways. Brand has described the standard procedures in 'Leprosy in Theory and Practice' edited by Dr R. G. Cochrane. A modification of the standard operation was tried by the author during 1958–61 while he was working at Purulia leprosy home and hospital.

Details of the author's modification: An incision is made from the medial condyle to the navicular bone and the tibialis posterior tendon is cut at its insertion. This is withdrawn through another incision made medial to the tibia five inches above the medial epicondyle. The third curved incision is made anteriorly to the front of the ankle joint. The flap is reflected and the deep

fascia longitudinally incised. The muscles are reflected and the interosseous space exposed. A window is prepared by removing the membrane for about two and half inches in its full width. The tibialis posterior is passed to the anterior aspect through the window in the interosseous membrane. The tibialis anterior, extensor digitorum longus and the extensor hallucis longus are identified and freed from the surrounding tissues without interfering with their continuity. With the knee flexed to about sixty degrees and the foot in maximum dorsiflexion the tibialis posterior is passed through the extensor digitorum longus and the extensor hallucis longus by the Pulvertaft method and then into the tibialis anterior tendon. A continuous stainless steel wire is used to suture these tendons and the raw end of the tibialis posterior buried in the tibialis anterior. The assistant should hold the foot in maximum dorsiflexion while the tendons are being sutured. A below the knee plaster is applied to maintain the foot in that position. The plaster is removed after four weeks. The patient is taught exercises for the re-education of the tibialis posterior for ten days without weight bearing and then weight bearing exercises are commenced and should be continued until the patient develops a normal gait.

The author performed over fifty operations on drop feet using the new method before he left for further studies in the United Kingdom in 1961. The range of movement is poor when compared with those done by the standard method. There were no inversion or eversion deformities in any of the cases and the position of the foot at rest was over a right angle.

The advantages of this operation are:

- 1.—The operation is easy to perform.
- 2.—Both the drop foot and the drop toes are corrected at the same time.
- 3.—The tendency to inversion or eversion deformities seems to be less than with the standard operation done by the circum-tibial route. This is due to the direct pull of the tibialis posterior on the foot. It is our impression that the correction of the drop foot by the interosseous route is always a better method than the circumtibial route.
- 4.—Bone is not interfered with as in the standard operation.
- 5.—Plaster is removed after four weeks as com-

pared with six weeks of immobilization following the standard procedure.

The operation by itself does not prevent ulceration but combined with restrictions to counteract the various other mechanical factors described above can reduce the recurrence of ulcers.

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# Experimental Human Leprosy in the Footpad of Mice

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Multiplication of *Mycobacteria leprae* in the footpads of mice has been reported by Shepard.<sup>10</sup> The increase has been up to 1,000 fold. Other workers like Chatterji<sup>4</sup> and Bergel<sup>3</sup> have also reported successful transmission of *M. leprae* in rats and mice by using different strains of animals and different food and technique. Mukherji<sup>6, 7</sup> has not been able to confirm their works. This work was undertaken to find out if Shepard's method of transmission of *M. leprae* in mice could be produced.

## MATERIAL AND METHODS

Earlobe biopsies from untreated cases of lepromatous leprosy were obtained after treating them with tinct. iodine and alcohol. These were cut in small pieces and ground up with sea sand in pestle and mortar with a little Hank's balanced salt solution containing 0.1 per cent bovine albumin. The suspension was lightly centrifuged. The supernatant was pipetted off and counted for mycobacteria by the method of Shepard.<sup>9</sup> It was diluted with Hank's balanced salt solution containing 0.1 per cent bovine albumin to a con-

centration of approximately  $10^5$  mycobacteria per ml. This diluted suspension in doses of 0.03 ml was injected subcutaneously into a single footpad of a hind leg of each mouse. Three groups of 20 mice each were inoculated with suspensions prepared from earlobe biopsies from three untreated lepromatous patients. Ten mice in each group were likewise inoculated in the footpads with 0.03 ml of suspensions containing  $10^5$  organisms per ml of *M. leprae murium* and *M. phlei*. The animals were kept in a room where temperature was maintained at approximately 30 °C. One mouse from each group was sacrificed every month and the footpad examined for mycobacteria.

Mycobacteria in the mouse pads were counted as follows: The footpads were washed with soap and water, rinsed with sterile water and dried with sterile gauze. The footpads were removed aseptically and cut into fine pieces with a pair of scissors. Each footpad was then ground up with sea sand in pestle and mortar with a little Hank's balanced salt solution containing 0.1 of bovine albumin under aseptic condition. Any mass of

## Results:

TABLE I

### Number of Mycobacteria in mouse footpad

	No. injected	Number recovered			
		1st month	2nd month	3rd month	8th month
<i>M. leprae</i>	$10^5 \times 0.03$	$10^5 \times 0.03$	$10^5 \times 0.025$	$10^5 \times 0.025$	0
<i>M. phlei</i>	$10^5 \times 0.03$	$10^5 \times 0.03$	$10^5 \times 0.03$	$10^5 \times 0.025$	0
<i>M. lepraemurium</i>	$10^5 \times 0.03$	$10^5 \times 0.03$	$10^5 \times 0.03$	$10^5 \times 0.07$	$10^6 \times 2.3$

TABLE II

### Tissue changes in mice liver and spleen

Time after inoculation	<i>M. leprae murium</i>	<i>M. leprae</i>	<i>M. phlei</i>
1 month	No change	No change	No change
2nd month	Collection of macro phages surrounded by lymphocytes	No change	No change
3rd month	Collection of macro phages surrounded by lymphocytes	No change	No change
8th month	Collection of macro phages surrounded by lymphocytes	No change	No change

unground tissue was removed by leaving the suspension at room temperature for several minutes. The process was repeated several times with Hank's balanced salt solution containing 0.1 per cent bovine albumin. All the fluids were collected and the total number of mycobacteria estimated using Shepard's<sup>9</sup> technique. Average counts only are shown in the results.

#### DISCUSSION

Mycobacteria could not be recovered from the footpads of mice receiving *Mycobacterium leprae* after eight months. Some acid fast bacteria could however, be recovered from the foot pads of mice receiving *Mycobacterium phlei* and *M. leprae* during the first three months. *Mycobacterium leprae* murium however, grow well in the mouse footpads and their numbers increased to over 700 fold.

Shepard's<sup>9</sup> work claiming increase of *Mycobacterium leprae* in mouse footpads could not be confirmed. It is possible, however, that the patients from whom materials were obtained were suffering from rat leprosy infection as has been found in some cases by several workers like Balfour Jones<sup>1</sup> and Burnet.<sup>2</sup> Otherwise the mice used in Shepard's work might have latent *Mycobacterium leprae* murium infection or might have got it in the laboratory as has been reported by Mukerjee and Kundu.<sup>8</sup>

#### SUMMARY

*Mycobacterium leprae* murium, *Mycobacterium leprae*, and *Mycobacterium phlei* were injected into mouse footpads in doses of  $10^5 \times 0.03$  per footpad. None of the Mycobacteria could be recovered from the foot pads of mice nor histological lesions found in

the livers and spleen of mice receiving injections of *M. leprae* and *M. phlei* in the foot pads.

#### ACKNOWLEDGEMENT

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# Anterior Transposition of Ulnar Nerve in Leprosy

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The scientific meeting on Rehabilitation of the Disabled in Leprosy held at Vellore, Madras State, India, during November, 1960 under the auspices of the W.H.O. recommended studies for further clinical research on peripheral nerves in general and ulnar nerve in particular.

On the subject of clinical research on the ulnar nerve, the scientific session agreed 'that ulnar nerve transposition anterior to the medial epicondyle and deep to the flexor mass, as far lateral as the median nerve, should be considered at the earliest sign of palpable enlargement of trunk, of pain, or of weakness. Where competent surgical help is not available, consideration should be given to simple unroofing of the olecranon groove or division of the tough fibrous band, crossing the nerve, where it leaves the olecranon groove. In the rare instances, where solitary lesions appear in major nerve trunks, consideration should be given to excision of the lesion as soon as it is quiescent with end to end anastomosis.'

Mention may be made of other peripheral nerves commonly affected in leprosy like the median, radial, lateral popliteal, posterior tibial and branches of the facial nerve. These nerves are not usually displaced. On the other hand, the ulnar nerve is transferred to a new anatomical bed. This is a distinguishing feature characteristic of ulnar nerve surgery and is mandatory.

Common to most of the sites of involvement in peripheral nerves are:

- (a) A superficial position.
- (b) Liability to trauma and pressure.
- (c) Proximity to bones and tendons.
- (d) Tendency to stretch on movement of joints.
- (e) A 'free lateral play' as in ulnar nerve.
- (f) Fibrous bands and tunnels distal to point of involvement.
- (g) Temperature lower than body temperature.

## SURGICAL ANATOMY OF ULNAR NERVE

### *Certain considerations*

Anterior transposition of the ulnar nerve is a well established surgical procedure. In general surgical practice, the indications are:

- (a) Gun shot injuries, resulting in extensive lesions to the ulnar nerve.
- (b) For all lesions in the post condylar groove (Traumatic neuritis).

*Note*—No mention is made of the ulnar nerve lesions in leprosy.

Of all the major peripheral nerves supplying the upper extremity the ulnar nerve is the most important as it innervates all the small muscles of the hand medial to the tendon of flexor pollicis longus. Besides, it also supplies both the heads of flexor carpi ulnaris and the medial half of the flexor digitorum profundus.

In the upper arm, at its middle, the nerve pierces the medial intermuscular septum, and accompanied by the long slender ulnar collateral artery, enters the posterior osteofacial compartment and descends along the medial head of triceps muscle being closely invested by its muscle fibres. No branches are given in the upper arm.

At the elbow it occupies the post condylar groove and under cover of the tough fibrous arch bridging the heads of origin of flexor carpi ulnaris. The bridge acts as a roof and the bony groove acts as floor, to which the nerve is adherent through loose areolar tissue.

The nerve then passes into the forearm between the heads of the flexor carpi ulnaris lying upon flexor digitorum profundus and under cover of flexor carpi ulnaris.

Thus the nerve is entirely posterior throughout. To transpose the nerve anteriorly the sharp tough fibrous barrier of the medial inter muscular septum has to be freely divided. During this division, the supratrochlear artery and its



branches may be severed, as it lies close to the medial inter muscular septum.

The next step is the division of the tough fibrous arch to unroof the nerve. To free the nerve from its bony floor, blunt gauze dissection of the areolar tissue is necessary.

Occasionally the nerve supply to the olecranon head of the flexor carpi ulnaris is high up, short, stout and effectively anchors the nerve rendering free mobilisation impossible. The branch has then to be sacrificed.

The nerve thus freed, is mobilised and brought on to the medial epicondyle where a muscle bed is provided by the division of the flexor mass. Angulation, kinking and undue tension of the nerve are avoided in the process of embedding it.

#### DISCUSSION

The series of 12 cases, constitutes a small record. They are presented here, as 3 out of 12 operated turned out to be nerve abscess.

The analysis of ulnar nerve case reports is as follows:

- (a) Secondary neuritis due to lepromatous leprosy —  $3 + 1 = 4$ .
- (b) Dimorphous —  $1 + 1 = 2$ .
- (c) Mono-neuritis multiplex — 2.
- (d) Solitary nerve abscess without any clinical skin involvement — 1.
- (e) Major tuberculoid — 3 (includes 2 nerve abscess).

Cochrane and Khanolkar have mentioned that there has been no evidence of the existence of pure polyneuritic or neuritic-sub type of tuberculoid leprosy. It is admitted that in all forms of leprosy — tuberculoid, lepromatous or dimorphous — the patient may show, in addition to visible cutaneous lesions, signs of general neural involvement. When the infiltration of the bacilli have disappeared from the skin, the neural signs remain as residual lesions resulting in secondary polyneuritic type. Muir and others have long held that neuritic leprosy is a true ascending neuritis, and the work of Khanolkar has indicated that this is in all probability correct.

Be that as it may, the nerve enlargement must be considered as an expression of active tissue response, with a tendency to localise, and in rare instances abscess formation does occur. The abscess may be either single or miliary and

multiple. It may be acute, sub-acute or chronic, and is usually chronic.

*Local epidemicological factors*: sub-type of the disease and age would appear to determine the incidence of abscess formation. This aspect is worthy of further elucidation. Also abscess formation in the ulnar nerve is more frequent than in other peripheral nerves. Mention may be made of Muir's three cases affecting the medial cutaneous nerve of the arm, the radial nerve and the ulnar nerve respectively.

'The remarkable thing about these three cases was that the lesions of the nerves affected were the only lesions discoverable in the body. Why abscesses should have formed in these cases it is difficult to say. Certainly it does not appear to be due to increased virulence of the causal organisms or to unusually low resistance of the tissues. Had that been so, then surely the disease would have shown manifestations in other parts of the body.'

#### SUMMARY

The directive principles as laid down in the WHO circular, in respect of emplacement of nerve in flexor muscle bed have been strictly adhered to.

The surgical importance of medial inter-muscular septum, ulnar collateral and supra trochlear arteries and branches are stressed.

In the case series reported no resection of nerve trunk was done and hence no 'tunnelling' of flexor muscle mass.

The role of nerve stripping is ambiguous — no trial was given to this surgical manouvre.

Intra neural injections of Novocaine, Rhondase, Dexamethasone and Priscol were restricted to mononeuritic cases and severe nerve trunk pain. Chymotrypsin was not tried owing to non-availability. These therapeutic measures are at best conservative and palliative.

The pus was always sterile.

One case of sutureless skin surgery with adhesive strips is reported. The cosmetic results are gratifying.

Post-operative follow up have included specific therapy, combined with long acting Sulfas, active and passive movements with massage and gradual weight bearing under supervision. The patients have been periodically reviewed at monthly intervals and are psychologically satisfied. There has been no clinical evidence of 'dislocation' of the nerve in its new anatomical bed.

In patients with paresis, atrophies and restriction in the mobility of joints, further development of these phenomena was discontinued.

Surgical intervention is the best method of prophylaxis of paralysis and deformity. This view expressed by Idris is shared by us.

#### ACKNOWLEDGEMENT

In conclusion I wish to thank the staff members of the Government Leprosy Subsidiary Centre, Kurnool, for their active interest and post-operative care of the patients. My particular thanks are also due to Sri M. Danaiah, Medico-social workers for his zeal and untiring efforts, Sri L. Ramaiah, B.A., for typing and to Dr C. Ramachandra Rao, M.B., B.S.SC., D.N. (Cal.), Chief District

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# A Patient with Semi-membranous Cyst in Leprosy Simulating Nerve Abscess

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## Case Notes

Dhanonjoy – a Hindu male of 23 was admitted into this colony in September 1963, as a L<sub>3</sub> case with high bacillary index.

He was anaemic on admission but was built up and made fit for anti-leprosy treatment. Treatment was given continuously and the treatment could be worked up to 150 mgs per week with short stop for two or three times for lepra reaction of minor degree. In January 1965, he started developing ENL – one crop after another came out and the specific treatment could hardly be given.

On 8th March 1965 he showed me one large and two small swellings on and above the middle of the popliteal fossa.

Clinically it appeared to be a nerve abscess and much interest was taken as nerve abscess in lepromatous cases are not common.

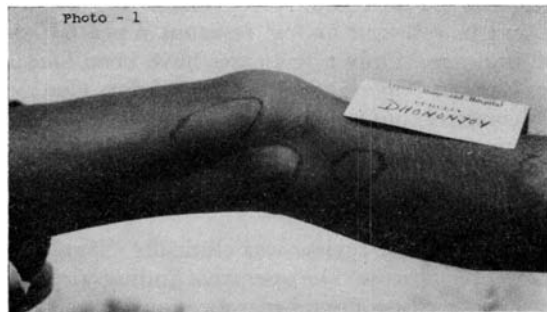


FIG 1 (8th March 1965)

One big and two small swellings on and above the middle of the popliteal fossa

On 10th April 1965 the small swellings disappeared, but the large one became larger.

Operation was decided upon with the following findings:

On incision and light dissection a tense cystic swelling bulged out in the upper part of the popliteal fossa and at the medial side of the mid line. It was easily detachable, but the upper portion became narrower to a pedicle and passed under the medial head of the gastrocnemius. It had no connection with any nerve. A tie was given round the pedicle and the cyst was removed. The case healed up uneventfully.<sup>1</sup>

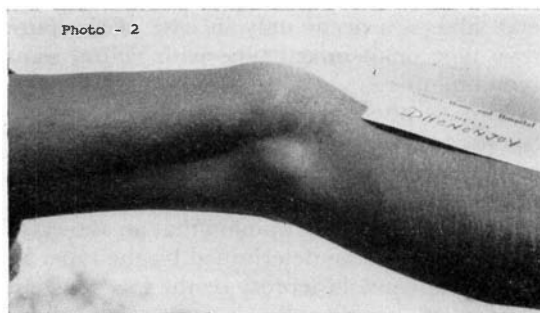


FIG 2 (10th April 1965)

Small swelling has disappeared but the large one become larger

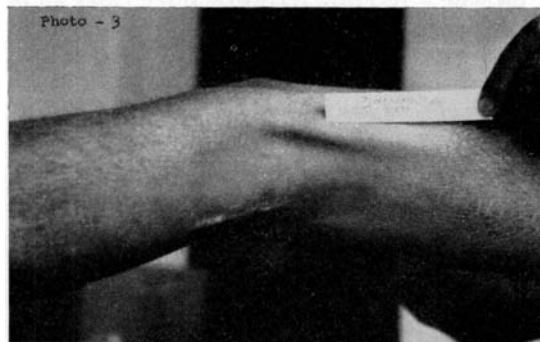


FIG 3

The cyst removed

The cyst was opened subsequently. It contained translucent jelly-like material.

## DISCUSSION:

It will not be out of place to recall the history and old discussions of the nerve abscess.

Muir – in 1924 – described two enlargements in the median nerve, one of them contained 10 c.c. of yellowish pus. He remarked that extremeswelling of the nerve often happens when

no other sign of the disease can be found. Pus contained no micro-organism.<sup>2</sup>

Lowe – in 1929 – reported about 2 per cent nerve abscess cases (100 in 5,000), and that these abscesses, Lowe associated with high resistance and the milder forms of the disease and often with lepra reaction. In many there were evidences of skin leprosy, nerve lesions predominating. The content was white or slightly yellowish, a semi solid cheesy substance, this containing lepra cells with lymphocytes, leucocytes.

Lowe also in earlier papers stated that the nerve abscesses occur only in case of the pure nerve type or of mixed type with neural signs predominating.<sup>2</sup>

Lowe – afterwards he prepared notes in response to an enquiry regarding certain cases of nerve abscesses wrote that this condition is seen almost exclusively in pure nerve type cases.<sup>2</sup>

Cochrane – is also of opinion that an abscess of the nerve should be determined by the type. In obvious tuberculoid leprosy or the low resistant variety, or occasionally in the dimorphous group in which the tuberculoid element is in marked ascendancy, swellings and pain of nerves should be investigated for nerve abscess.<sup>3</sup>

Browne – recently recorded three cases all of whom were suffering from major tuberculoid leprosy.

#### *Incidence of nerve abscess – country wise*

Wade – is of the opinion that abscess of the nerve is a particularly interesting feature of leprosy in India.

Browne – reported only three cases of nerve abscess out of his 8,000 patients in Eastern Nigeria. In 1957 he reported two instances in some ten thousand leprosy patients seen in the Belgian Congo.<sup>4</sup>

Wheate – has recently drawn attention to the rarity of so called nerve abscess in Africa.

Lowe – in 1929/34 reported an incidence of 2 per cent (100 – 5,000) among 5,000 patients.

Nerve abscess is not infrequent as has been found outside of India.

Multiple abscess in the same nerve are also not very uncommon.

Findings in fluid – it is very interesting to note the differences in findings of the fluid out of the abscess. Muir did not find any micro-organism and the pus caused no infection in guinea pigs. Browne in one of his cases found collection of acid fast bacilli. Lowe also found lepra cells in the fluid along with Leucocytes and Lymphocytes.

Incidence of nerve abscess in the resistance and low resistance cases (tuberculoid and borderline cases) has been agreed by all writers though Lowe once mentioned that in many cases there were evidences of skin leprosy but nerve lesions predominated.

#### OPERATION

The contents of the abscess should be evacuated in time. Delayed operations have often revealed all the neurons caseated and divided and the continuity of the nerve was only by the nerve sheath. Brand casts doubts on this procedure and says surgical interference causes further damage.<sup>3</sup> In the practical field it does not hold good.

#### SUMMARY

While nerve abscess are rare outside India, can often be met in India. Nerve abscess are usually found in resistant or less resistant repeated reacting cases. Only a few cases have been found in Eastern Nigeria and in the Belgian Congo. Wheate also has recently drawn attention to the rarity of the so-called nerve abscess in Africa.

#### CONCLUSION

The case under review was clinically diagnosed as a nerve abscess. The operative findings proved it to be a case of semi-membranous cyst. This confirms the view that nerve abscesses occur in resistant type of leprosy cases only.

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# Treatment of Leprosy with a Combination of Injectable Thiambutosine (CIBA 1906), Streptomycin and Isoniazid

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In previous trials done at the Westfort Institution, oral thiambutosine (CIBA 1906, diphenylthiourea) has been shown to be as effective as dapsone in the treatment of leprosy. (Davison, 1965). Intramuscular injections have a similar effect. (Browne, 1965). The results obtained with the use of anti-tuberculosis drugs, including streptomycin and isoniazid in leprosy are 'equivocal and on the whole, disappointing' (Cochrane and Davey, 1964). As far as we know there are no previous reports of the treatment of leprosy with a combination of thiambutosine, streptomycin and isoniazid. In 1963 Dr B. A. Dormer, Advisor on Tuberculosis to the State Health Department, Republic of South Africa, found that intramuscular thiambutosine plus streptoneotizide injections (containing streptomycin sulphate and sodium methane-sulphonate of isonicotinic acid hydrazide) gave better results than any previous treatment in human and animal tuberculosis. (Dormer, 1963). At his suggestion a similar form of combined treatment was tried on leprosy patients at the Westfort Institution.

## METHOD

The project consisted of three groups of lepromatous patients, each group being equal, as far as possible to the other with regard to the clinical and bacteriological status and previous treatment with dapsone. Treatment was continued for one year in each group.

Patients were examined and photographed at the start of the project, and clinical and bacteriological examinations were repeated at monthly intervals.

Lesions, i.e. infiltrations, macules and plaques

were graded according to severity from 0 to 3 in three sites each (face, trunk and limbs). The maximum lesion index possible was therefore 27.

The Bacteriological Index was obtained from the results of scrapings taken from four sites, and graded from  $\frac{1}{2}$  to 4 each, the maximum therefore being 16.

The presence of erythema nodosum leprosum was recorded at each monthly examination.

The number of patients and the treatment received in each group was as follows:

<i>Group</i>	<i>Number of Patients</i>	<i>Treatment</i>
A	17	Dapsone
B	15	Streptomycin and Isoniazid, thiambutosine, Dapsone
C	14	Streptomycin and isoniazid, thiambutosine

## DOSAGE

The dose of dapsone was 100 mgm daily for six days a week.

For the first five weeks patients in group B and C received bi-weekly Streptoneotizide injections (Erba) with a total of 4 g streptomycin sulphate and 2.4 g sodium methanesulphonate of isonicotinic acid hydrazide per week. As the injections were extremely painful they were stopped and streptomycin 4 g weekly and isoniazid tablets 3.6 g weekly were given instead for the rest of the year.

Thiambutosine 2 g was given in a single weekly intramuscular injection in one site. (During the year's treatment two sterile abscesses occurred).

## RESULTS

The lesion and bacteriological indices before and after treatment are presented in Table I. It can be seen that the lesions regressed in all groups with no significant difference between them. In Group A which received dapsone alone, the average fall in the bacteriological index after treatment, was greater than in the other two groups.

E.N.L. occurred in all groups during the year of treatment. It was most frequent in the group receiving dapsone alone. However, the number of patients is too small to draw any conclusions about the incidence of E.N.L. in the different groups.

TABLE I  
Results After One Year of Treatment

Group	Number of Patients	Average Lesion Index		Average Bacteriological Index	
		Before	After	Before	After
A	17	4.7	4.0	15.2	10.6
B	15	5.2	3.9	14.9	13.0
C	14	6.1	5.1	14.6	13.5

## SUMMARY AND CONCLUSION

Twenty-nine patients with lepromatous leprosy were treated with a combination of injectable thiambutosine, streptomycin and isoniazid, for one year. This treatment was not found to be more effective than dapsone alone.

## ACKNOWLEDGEMENT

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# A Study of Lepromin in Healthy Contacts

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The Lepromin test is the only test in leprosy patients which expresses the immunity and diagnosis of the patient. It has been widely used by leprologists, but comparatively less has been done to study the effects of lepromin on healthy contacts. This paper reports an attempt of a study of this nature.

## *Selection of patients*

The Control Unit in Chilakalapalle has a training centre attached. We selected some of the trainees who came from highly endemic areas.

## *Actual procedure*

1 ml of refined lepromin was injected intradermally in the ventral surface of the forearm, using a sterilised tuberculin syringe and changing the needle after every injection. First reaction was usually a raised, red indurated area of 10 mm diameter in 24 to 48 hours. This indurated area began to disappear from the fourth day onwards and resolved completely. The site became slightly painful and tender again after two weeks and a firm nodule appeared which was also slightly painful and tender in most patients. In some patients the nodules burst and freed a discharge and the nodule in a few patients took more than two weeks to heal. The discharge was stained by carbol fuchsin in a few patients and examined microscopically. The following notes give the results of 25 patients:

1. Male 27 years – size of early reaction 50 mm; the late reaction consisted of a nodule of 5 mm in diameter which burst producing an ulcer which liberated cheesy material which healed in three weeks. The patient had been working as an assistant in a leprosy hospital for the last five years.
2. Male 25 years – the early reaction was 24 mm in diameter; the late reaction was a nodule of 4 mm in diameter which became an ulcer and which healed in nearly three weeks. The patient had been working as an assistant in a leprosy hospital for nearly six years.
3. Male aged 25 years – early reaction was a nodule of 32 mm diameter; the late reaction was an indurated area succeeded by an ulcer which healed in three weeks.
4. Male aged 28 years – early reaction was a nodule of 24 mm; the late reaction was an indurated area followed by ulcer formation which healed in three weeks.
5. Male aged 24 years – early reaction was a nodule of 41 mm; the late reaction was a nodule of 4.5 mm which gradually subsided. The patient had been working in a leprosy hospital for the last two years.
6. Male aged 23 years – early reaction was a nodule of 45 mm; the late reaction was an indurated area which gradually subsided.
7. Male aged 20 years – early reaction was a nodule of 15 mm; the late reaction was an indurated area which gradually subsided.
8. Male aged 27 years – early reaction was a nodule of 25 mm; the late reaction was a nodule formation of 4 mm which healed without ulcer formation. The patient had been working as a peon (messenger) in the unit for the last nine years.
9. Male aged 45 years – early reaction was a nodule of 28 mm; late reaction was a nodule of 4 mm which healed smoothly. The patient had been working as a peon in the unit for the last 11 years.
10. Male aged 24 years – the early reaction was a nodule of 28 mm; the late reaction was an indurated area which gradually subsided. The patient is on the staff of the unit.
11. Male aged 20 years – the early reaction was a nodule of 20 mm; the late reaction was an indurated area which gradually subsided. The patient was watchman of the Unit for three years.



12. Female aged 29 years – the early reaction was a nodule of 14 mm; the late reaction was an indurated area which gradually subsided. The patient was on the staff of the unit for the last three years.
13. Male aged 20 years – the early reaction was a nodule of 18 mm; the late reaction was an indurated area of 50 mm. The patient worked for one year in the Unit.
14. Male aged 22 years – the early reaction was a nodule of 14 mm; the late reaction was an indurated area of 13 mm. The patient worked for three years.
15. Male aged 21 years – the early reaction was a nodule of 12 mm; the late reaction was an indurated area of 10 mm. The patient worked for one year.
16. Male aged 21 years – the early reaction was a nodule of 12 mm; the late reaction was an indurated area of 10 mm. Still working in the Unit.
17. Male aged 19 years – the early reaction was a nodule of 16 mm; the late reaction was an indurated area of 9 mm.
18. Female aged 22 years – the early reaction was a nodule of 16 mm; the late reaction was an indurated area of 10 mm.
19. Male aged 20 years – the early reaction was a nodule of 10 mm; the late reaction was an indurated area of 8 mm.
20. Male aged 19 years – the early reaction was a nodule of 10 mm; the late reaction was an indurated area of 8 mm.
21. Male aged 22 years – the early reaction was a nodule of 19 mm; the late reaction was an indurated area of 6 mm.
22. Male aged 22 years – the early reaction was a nodule of 10 mm; the late reaction was an indurated area of 6 mm.
23. Male aged 27 years – the early reaction was a nodule of 11 mm; the late reaction was an indurated area of 5 mm.
24. Male aged 22 years – the early reaction was a nodule of 19 mm; the late reaction was an indurated area of 8 mm.
25. Male aged 21 years – the early reaction was a nodule of 14 mm; the late reaction was an indurated area of 10 mm.

#### SUMMARY

Some 30 paramedical workers and staff workers of Chilakalapalle Control Unit (originating from different parts of India), who came for leprosy training were selected and took part in an experiment to study the results of the lepromin test in healthy contacts. It was found that all subjects reacted positively and in some the late reaction was pronounced and an ulcer developed on this site of inoculation.

#### DISCUSSION

It is now well known that most healthy contacts of leprosy suffer from repeated subclinical infection and by means of it acquire immunity against leprosy. The contact of the above subjects with a leprosy patient from time to time had apparently allowed a small number of leprosy bacilli to enter the body and so stimulate the histiocytes to minimum control of the vascular and to the limitation of the infection. The experiences seem to have stimulated the defence mechanism so that it reached its peak at the age of 20 years. The resistance seems more evident in those who work in the field of leprosy for some years, perhaps because they come into more intimate contact with leprosy patients in such a way that greater degree of immunity can evolve. It follows that carrying out lepromin testing in endemic areas will assist in detecting those who have not acquired immunity against leprosy and enable precautions to be taken against any dangerous degree of contact. The lepromin test itself is, of course, valuable in the prevention of leprosy when carried out with discretion and ingenuity.

# Result of Marianum Antigen in the Treatment of Leprosy

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## INTRODUCTION

We present a report on patients who were treated principally with Marianum Antigen at eight small leprosaria and 70 treatment stations in six provinces of Korea at least once a month by stationary and mobile clinics.

The total number of patients was over 11,000 listed by seven doctors, among whom 6,605 were registered by Drs Bagalawis, Oh and Whang, who worked a much longer term than our other doctors, but for this paper only 2,869 were selected who came regularly for treatment and observation up to 7½ years. Of the 2,869 treated, 2,502 had M.A. therapy and the other 367 cases were divided into two therapy groups for comparison. The great majority omitted from this report were inmates of leprosaria given over to other control, or wandering patients, forced from place to place by the public or the police, of whom track was lost. Many expecting too rapid a cure came and went then disappeared; and some died.

Except 687 living in leprosaria nearly all of the 2,869 were home patients. They were treated at 70 stations; many of them had no shelter except bridges and crematoria, so that often the patients were exposed to bad weather and to the curiosity of passers-by. Advanced patients usually could not use public transport some having to walk up to 10 miles. But all cited here were faithful in meeting our clinics at fixed places, days and hours.

The majority had no previous care from any doctor and had only self-treatment, if any. Few have means to support themselves. Some work hard as day-labourers, some have to beg for their living. Without the monthly food supply, which we try to distribute, about 20 lbs of grain, many would verge on starvation.

Most of the wandering patients had been in leprosaria under sulphone therapy. Some were discharged as negative patients and nearly all were stationery patients but often needing care for concurrent diseases. Some had narcotic or alcoholic habits and had gone off as wandering beggars. Home patients in fear of segregation shun government officials.

Mobile clinics seem to be the best means of taking care of these patients, to examine their contacts in view of early treatment, to follow up suspicious cases and to prevent the spread of the disease.

## METHOD EMPLOYED

- Group A* . . M.A. – Marianum Antigen
- Group B* . . DDS – sulphone
- Group C* . . M.A. + DDS – Marianum Antigen and sulphone.

The usual dose of Marianum Antigen was from 0.03 to 0.1 ml, given by intradermal injection in the deltoid region of the shoulder, once a month for periods of six months, and occasionally stopping for a month.

In Group B and C the initial dose of DDS was 50 mg a week given orally for the first two weeks; 100 mg a week for the second two weeks, with a gradual increase until the maximum dose of 600 mg a week was reached.

Clinical examinations, dermatological and neurological, were made by the doctors once a month, while bacteriological examination, generally, was made only in the lepromatous type by the modifications of Wade's method two to four times a year.

TABLE I

## Classification of Patients by Clinics

Group	No. of Patients Participating			Total
	Dr Bagalawis's Clinic	Dr Oh's Clinic	Dr Whang's Clinic	
Group A on M.A.	509	1,548	445	2,502
Group B on DDS	196	71	17	284
Group C on M.A. plus DDS	83	—	—	83
Total	788	1,619	462	2,869

Of the total number of patients in the three clinics, approximately two-thirds were males; most of the patients were between 10 and 50 years of age. The ratio of lepromatous to tuberculoid types was 1.3 to 1.

## CLINICAL RESULTS

The clinical results were summarized as 'Improved' (arrested, markedly or moderately), 'Stationary' or 'Worse'.

In the above table the respective proportion

TABLE II

Therapy Group and Type of Disease		No. of pts.	Dr Bagalawis's Clinic			No. of pts.	Dr Oh's Clinic			No. of pts.	Dr Whang's Clinic		
			Impr.	Stat.	Worse		Impr.	Stat.	Worse		Impr.	Stat.	Worse
A	L	311	72%	17%	11%	758	69%	29%	2%	288	67%	30%	3%
	T	198	60.6%	31.8%	7.6%	790	66%	33%	1%	157	51%	49%	
	Total	<b>509</b>	67.8%	22.6%	9.6%	<b>1,548</b>	68%	31%	1.0%	<b>445</b>	61%	37%	2%
B	L	126	66%	25%	9%	44	63.6%	31.8%	4.6%	14	57%	43%	—
	T	70	49%	47%	4%	27	52%	48%	—	3	67%	33%	—
	Total	<b>196</b>	60%	33%	7%	<b>71</b>	59%	38%	3%	<b>17</b>	59%	41%	—
C	L	68	72%	16%	12%								
	T	15	73%	20%	7%								
	Total	<b>83</b>	72%	17%	11%								

classified as 'Improved', 'Stationary' and 'Worse' is about the same in each clinic, according to the mode of therapy. On the average 66.5 per cent of the patients were improved in Group A, 59.5 per cent of the patients were improved in Group B, while in Group C, 72 per cent of the patients were improved. The difference of improvement

between Group A and B averages approximately at 7 per cent — Group A — Marianum Antigen — was more effective than Group B on DDS.

Percentages of 'Arrested' patients out of the 'Improved' — in relation with the length of time of treatment in Dr Oh and Dr Whang's clinics are as follows:

TABLE III

<i>Duration of Treatment (Year)</i>	<i>Dr Oh's Clinic</i>		<i>Dr Whang's Clinic</i>	
	<i>No. of improved</i>	<i>No. of arrested (per cent)</i>	<i>No. of improved</i>	<i>No. of arrested (per cent)</i>
1st Year	220	—	48	—
2nd Year	235	0.4%	58	1.7%
3rd Year	198	20.2%	43	27.9%
4th Year	151	51.1%	51	56.9%
5th Year	133	83.7%	37	67.6%
6th Year	85	88.2%	34	94.1%
7th Year	25	92.0%	2	100.0%
Total	1,047	25.1%	273	37.0%

(Arrested patients were defined according to the description of the 'Inactive' cases adopted by the VIIth International Congress on Leprology in Tokyo).

Although the proportion of 'Arrested' patients is remarkably increased after 2½ years treatment, there is a big difference of percentages obtained in the two clinics – 25 per cent of Dr Oh's

patients, against 37 per cent for Dr Whang's. Such difference may be related to the stage of the disease among the selected patients.

Table 4 shows percentages of improvement obtained among Dr Bagalawis's patients, according to the duration of treatment (three years) in the different therapy.

TABLE IV  
Therapy Groups

<i>Duration of Treatment</i>	<i>A. on M.A.</i>		<i>B. on DDS</i>		<i>C. on M.A. and sulphone</i>	
	<i>No. of patients</i>	<i>No. of Impr. (per cent)</i>	<i>No. of patients</i>	<i>No. of Impr. (per cent)</i>	<i>No. of patients</i>	<i>No. of Impr. (per cent)</i>
1st Year	316	62.0%	80	53.7%	29	58.6%
2nd Year	122	71.3%	76	59.2%	31	71.0%
3rd Year	35	77.1%	39	71.8%	14	85.7%
Total	473	65.5%	195	59.5%	74	68.9%

In the above Table, improvement is obtained more rapidly in Group A than in Group B, in the first three years of treatment; but Group C shows a higher percentage of improved cases, than the other two groups for the same length of time.

Leprosy reaction was present during the course of treatment in 20.7 per cent (E.N.L. 25.2 per cent, and 16.3 per cent of reaction in tuberculoid cases) of Dr Oh's clinic; and 32.1 per cent of Dr Whang's clinic in Group A; they occurred more frequently in the first to second years of treatment, without any clear relationship to the therapy group.

Ocular complications were present on preliminary examinations in 158 patients in Dr Oh's clinic, and 58 patients in Dr Whang's clinic.

The clinical results of these patients were as follows:

DR OH'S

66 improved; 79 stationary; 13 worse

DR WHANG'S

8 improved; 35 stationary; 15 worse

The loss of eyebrows was commonly seen in lepromatous patients; among the patients classified as 'Arrested' in Group A, 63 patients in Dr Oh's clinic, and 41 patients in Dr Whang, had

their eyebrows grown again, while none was observed in Group B patients.

Gynaecomastia was recorded as healed in four patients out of 12, by Dr Oh; and 10 patients out of 13 by Dr Whang, in Group A, without any sexual hormone treatment.

The general condition of the patients remained good in all therapy groups, even among those classified as 'Stationary' in all the clinics.

For the bacteriological examinations of lepromatous patients, smears were taken from both sides of the nasal septum, both earlobes, and other optional skin sites, and subsequent smears were from approximately the same areas. The present

analysis deals only with Group A, in the preliminary and final results.

Three grades in a positive finding were designated as follows:

Negative	..	no bacilli found in 100 fields.
One-plus	..	rare, one or less than one bacillus in each microscopic field.
Two-plus	..	numerous, bacilli found in all field.
Three-plus	..	abundant, many bacilli in all field.

TABLE V

### Bacteriological Findings on Preliminary Examination

<i>Results</i>	<i>Dr Oh's Clinic</i>	<i>Dr Whang's Clinic</i>
Negative	168 (22%)	55 (19%)
Positive +	332 (44%)	112 (39%)
Positive ++	175 (23%) 590 (78%)	74 (26%) 233 (81%)
Positive +++	83 (11%)	47 (16%)
Total	758 (100%)	288 (100%)

Seventy-eight per cent of all lepromatous patients were positive at the outset as by Dr Oh, compared to 81 per cent by Dr Whang. Of all positive patients who completed treatment, the proportions becoming negative were 83.6 per cent (493) by Dr Oh and 82.8 per cent (193) by Dr Whang. The remaining patients were never heavily positive except 12 of them by Dr Oh and nine of them by Dr Whang.

### DISCUSSION

In the treatment of leprosy, Marianum Antigen was given for large scale trials by stationary and mobile clinics, while the other two groups (Group B on DDS and Group C on M.A. plus DDS) were used for control.

Comparing the results in the three therapy groups, Group C on M.A. plus DDS which was experimented by Dr Bagalawis, has shown better results than the other two therapy groups, however the number of selected patients was too small and no significant control group was made by any doctor. Therefore, it may be advisable to have more experimental study in the future.

The results between Group A on M.A. and Group B on DDS Group A was slightly better benefit than Group B. On the average 66.5 per cent of the patients were clinically improved in Group A, against 59.5 per cent in Group B.

The proportions recorded as stationary were relatively high at all clinics. The reason seems due to the different concept of the doctors for the state of the disease and also there are many difficult problems to judge clinical change in patients. These patients who were classed as stationary may be either improved or arrested.

The present paper includes some inmates of the leprosaria treated by Dr Bagalawis and most of them received prior to sulphone therapy. Thus clinical changes were recorded considerably more frequent in patients with prior sulphone treatment than in others.

During the treatment at the stationary and mobile clinics, 25 patients who had gynaecomastia were treated on M.A. alone without any sexual hormone. Out of 25, the symptoms of 14 patients were healed or disappeared, however it is doubtful whether the improvement was attributed to therapy or not.

In the majority of the patients who received M.A. treatment, there appeared at the injection site an erythematous papule (sore). After that, it showed an ulcer sometimes due to secondary infection, but it healed with scar within the month. A few patients had lymphangitis in the local area and a less number had general reactions such as: fever, headache, dizziness and rarely pruritis, etc., but these usually disappeared after a few days to two weeks.

The patients have been supplied with food and relief goods when possible. It would be very helpful for patients to be treated regularly.

It was found that M.A. therapy is more effective for patients visited once or twice a month by mobile clinics than sulphone drugs administered orally, because M.A. is non-toxic and the doctor controls the exact dosage.

#### SUMMARY

- (1) This is a controlled study of leprosy patients which was carried out by stationary and mobile clinics using the antigenotherapy of Marianum Antigen. Among 6,605 registered by three of seven doctors, 2,869 were selected for the report. Out of 2,869, 2,502 were treated with M.A. up to 7½ years in standard dosage, 287 with only DDS and 83 received M.A. plus DDS for comparison.
- (2) Both M.A. and DDS therapies were well tolerated. In this study the Group on M.A. showed slightly better clinical improvement than the Group on DDS. The clinical effect of M.A. is seen in the following results: 4.2 per cent did not benefit; 30.2 per cent remained stationary; and 65.6 per cent continued to improve in general conditions and in specific lesions such as: infiltration, nodules, ulcers, maculae, nerve enlargement and others until arrested.
- (3) The lepromatous type showed higher proportion of improvement than tuberculoid type. To the patients who became arrested after 2½ years on M.A. a maintenance dose was given for the next three or four years. *No relapse occurred.*
- (4) No evidence was obtained that clinical improvement may be related to age or sex.

- (5) In the lepromatous type 83.4 per cent among the patients who were bacteriologically positive were converted to negative.

- (6) Patients with leprosy reaction or ocular complications received about a half the standard dosage of M.A. or DDS with symptomatic treatment, usually with beneficial effect.

This report was compiled and edited by Shi Riong Choi, M.D. and D.P.H. Leprologist of R.O.K. Ministry of Health and Social Affairs, after careful study of the voluminous reports of Drs Bagalawis, Oh and Whang, and of thesis charts on individual patients.

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# “Hyfrecator”<sup>\*</sup> Sparking in the Management of Leprosy

## **An Auxiliary Treatment**

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‘Hyfrecator’ sparking has been found to be very useful in the treatment of many skin disorders and the writer has developed various specialized techniques of this procedure over the last seven years (Tio, to be published).

In 1964 the writer applied this method in two leprosy patients of long standing, essentially as a psychological prop to bolster up the patients’ morale. The patients’ statements, however, indicated a far greater improvement than could be explained on purely subjective grounds. And the writer himself got the impression that perhaps the sparking procedure really had had a favourable influence on the lesions.

In January 1965 the writer had occasion to apply this treatment to anaesthetic patches of seven years standing. The response in this patient was truly dramatic and after about two weeks of intensive sparking, normal sensation returned to all the areas treated. Since this patient was an intelligent woman the writer was now convinced that the method had a definite place in the management of leprosy. Subsequently the writer tried out the method in a few other cases in his private practice with less dramatic but nevertheless remarkable response. This experience encouraged the writer to carry out trials with this method on a large scale in the out-patient department of the Institute.

### *Instrumental technique*

The ‘HYFRECTOR’ is essentially a high frequency spark-gap diathermy instrument which is provided with a variety of needles, the points of the needles normally being used for coagulation, desiccation and fulgurization. By holding the needle-point a short distance away from the skin a spray of sparks is produced. For obtaining a broad spray for treating larger areas the writer has used the shaft (and the back of the angle) of the curved desiccation needle No. 711B. The intensity of the sparks can be controlled by turning

the adjustment knob on the instrument. On the recommendations made by the writer the manufacturers have made special modifications of the needles for the sparking technique which hitherto had not been used by any other worker. The modifications consist mainly of making the needle end in a ball. This ball permits the spraying of lesion in awkward locations. Further modifications of the needles in consultation with the writer are being made.

### *Precautions*

In employing the sparking technique it is important to guard against three hazards:

- unsteadiness of the operator’s hand;
- the patient’s liability to move the target area;
- the liability of the town’s electricity supply to vary in voltage.

The spraying of sparks give rise to a heat sensation and this can be very unpleasant for the patient, especially on the face. On anaesthetic areas, of course, this problem does not arise. The heat sensation can be made bearable by blowing of cooled air from a hair-dryer on the area being treated.

The investigations carried out in the Institute were planned with the purpose of evaluating the effects of sparking on a variety of skin lesions and the results are similarly favourable.

### *Patients*

Most of the patients were obtained from the male outpatient clinic of the National Institute of Health Surabaya. Only those who showed symmetrical similar lesions were selected for this investigation. (From the private clinic some were treated by the method as described below, others were sprayed with sparks on all lesions).

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<sup>\*</sup>Trade mark of the Birtcher Corporation, 4371 Valley Blvd., Los Angeles 32, California, U.S.A.



### *Technique*

Sparks were sprayed on leprosy lesions on the left half of the body only, the other side of the body serving as control. The evaluation can be divided into two categories:

- (a) *Visible changes*, viz., diminishing of the lesions in redness, size and thickness. This includes the *aesthetic* aspect of the treatment of leprosy.
- (b) *Functional changes*, viz., the return of the normal functions of the skin such as:  
sensations – touch, heat and pain,  
secretion of the sweat and sebaceous glands, (re)growth of hair.

### *Special Cases*

In addition to the selected patients in the Institute, the writer has treated several patients in his private practice, some of which are of special interest and as such brief reports on these cases are given below.

D. Female, 31 years, first examined January 1963. History: discoloured spot seen on right thigh in 1958.

Clinical findings: other discoloured hypo-aesthetic spots discovered on the back, buttocks and near anus. Despite the long duration this was a mild case.

Diagnosis: M. Hansen T-type.

Therapy: Sulphones caused drug fever and giant urticaria; therefore discontinued. Put on CIBA 1906 and later additional Vadrine.

No improvement seen after one year and spot on the right thigh actually increased in size. January 1965 two weeks of intensive sparking (3 x a week heavy doses) resulted in complete return of all sensation.

Maintenance sparking continued 1 x week till July when patient left town.

Re-examination on 5 September 1965: all areas had normal sensation.

*Note:* Hypo-aesthesia had existed for over seven years and only two weeks of the intensive sparking treatment caused a return of normal sensation.

L.T.T. Male, 20 years, first examined 9 April 1963. Clinical findings: anaesthetic patches right arm and right thigh.

Duration 10 years. Patient's account of therapy received very vague, presumably had

been on Sulphones, since he had seen other dermatologists.

Diagnosis: M. Hansen T-type.

Sulphones prescribed, visits infrequent.

20 December 1964 some return of sensation noted. Progress considered very slow.

Sparking begun and repeated whenever the patient could visit – on an average once every two months. Return of sensation much more rapid in spite of infrequent spraying.

N.T.P. Male, 42 years, first examined 7 July 1965. Clinical findings: erythema cheeks; extensive anaesthetic areas with red annular margin on thighs.

Duration?

Diagnosis: M. Hansen T-type.

June 1965 put on Sulphones by a colleague; July 1965 no improvement.

After first sparking redness of margin reduced and sensation returned.

Sulphone dosage increased.

24 July sensation practically normal, margin of patches turned violet-brown.

Patient gone away to home island.

P.T.S. Male, 29 years, first examined 4 March 1964. Clinical findings: large anaesthetic area right leg.

Duration?

Diagnosis: M. Hansen T-type.

Sulphone therapy started; patient not seen again till May 1965. 17 May 1965 St.q.a; weekly sparking started; after two weeks heat of sparking felt; during three months of fairly regular sparking all sensations gradually returned, first in the upper part and later the lower part. 20 August 1965 all sensations practically returned to normal.

T.K.B. Male, 31 years, first examined 24 August 1960. Clinical findings: red plaques on body.

Duration three years.

Diagnosis: M. Hansen T-type.

Therapy: Sulphone therapy with several interruptions during which his condition used to get worse. During 1964 additional sparking therapy was given and this speeded up the recovery (disappearance of lesions, return of sensations) as compared with the time needed for the subsidence of previous exacerbations with Sulphones alone.

*Comments on the results obtained*

(a) The regression of all types of visible *leprosy lesions* in colour, size and volume including the reactionary lesions is of importance from the aesthetic (psychologic) point of view.

(b) *Speeding up the return of sensation*: the first to return is the thermic sensation; sparking can be felt by the patient more and more strongly. Afterward tactile (cotton wool) and pain (pin prick) sensations seem to come back simultaneously.

(c) *Sweat and sebaceous glands are both stimulated by sparking*: sometimes the sweat glands respond immediately during the sparking session although the restoration of normal function may take some time. Sebaceous glands, on the other hand, seem to start functioning normally sooner than the sweat glands. Remote indirect stimulation of sweat glands: sparking of the L pectoral area also induced the sweat glands on the R pectoral side to produce more sweat (Figs. 1, 2, 3 and 4).

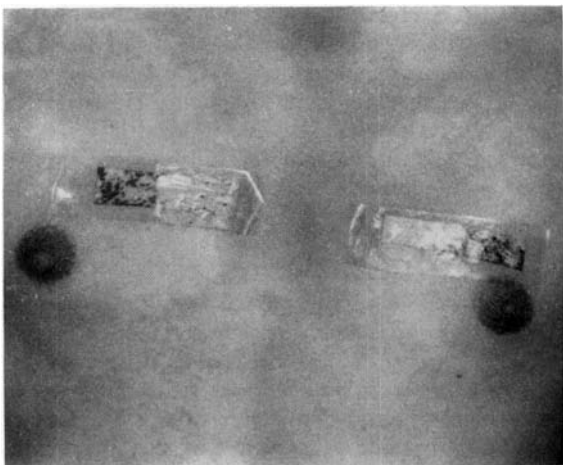
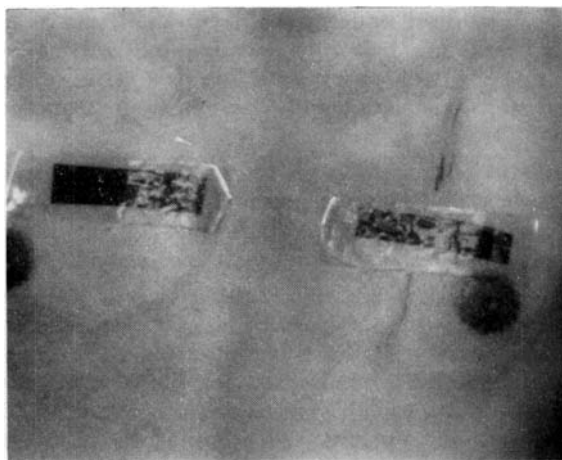


FIG. I. CASE 7.

Before sparking. Starch-iodine paper strip and negative Goenawan's copying pencil test.



III. CASE 7.

Five minutes after sparking. Starch-iodine test and copying pencil test (performed on the left side only)

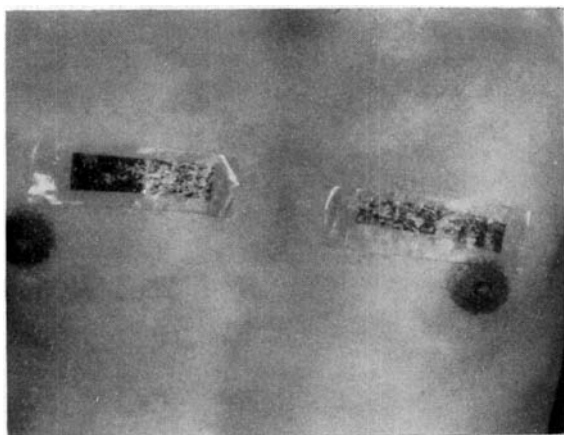


FIG. II. CASE 7.

Starch-iodine test immediately after sparking left side only. (Note response also on opposite side)



CASE II.

Before sparking face, ears and hands on both sides were affected. Picture taken on 29/9/65 after 5 months of regular weekly sparking.

(d) The endorgans of the nerves respond earlier to sparking than the sweat glands.

(e) In one case improvement of sensation (thermic, tactile as well as pain) occurred after one sparking treatment only, as compared to the control side.

(f) Sparking also seems to influence the *nerve* itself; not only the diameter became smaller, its consistency also got softer. It is noteworthy that the nerve itself was not sparked but only its neighbourhood.

(g) In three patients the *eyebrow* hair started to grow again. This may be caused by the stimulating effect of sparking itself or as a result of the regression of lesion and relief of pressure from the infiltration or both.

(h) With regard to the return of sensation there seems to be one example of failure after six months' of fairly regular sparking treatment. The disease was of long standing (20 years).

(i) In one patient one fairly large red area was sprayed with sparks while half of this area got an additional 5 mg Cortisone injection s.c. The injected half became less red but sensation did not return as quickly as in the other half. Did Cortisone suppress the stimulating effect of sparking?

#### DISCUSSION

(1) The loss of functions of the endorgans of the nerves, the sweat and sebaceous glands and loss of hair is assumed to be caused by the pressure of infiltration of round cells. The restoration of these functions combined with the regression in size and volume of the lesions suggests that spraying of sparks diminishes the infiltration thus relieving those organs from the pressure of them.

(*Note:* so far, for technical reasons, no biopsies before and after sparking treatment could be performed).

(2) It seems possible that the quantitative esti-

mation of the function of the sweat glands (paper strip technique) and of the sebaceous glands (so far technically not possible) can be used as *indicators* with regard to the *prognosis*.

(3) Dr Araujo in Brazil has used galvanocautery for making multiple skin punctures by fulguration (as a substitute for intradermal injections) to introduce hydrocarpus into the skin (Muir, p. 121). Dr Araujo's technique would seem to bear no similarity with the 'sparking' procedure described in this paper.

(4) The writer feels that, because of its simplicity and effectiveness, the sparking procedure has a definite place in the management of leprosy. This auxiliary treatment could be adapted even for mass campaigns in the field. However, a heavy-duty model of the apparatus will be necessary for large scale continuous use in the field, as the present type of the instrument tends to get overheated when used for long periods.

#### SUMMARY

A new sparking technique with a high frequency diathermy apparatus has been described. Favourable influence on the skin lesions of leprosy by the local application of 'Spark-spray' have been kept in over 40 patients. Records of the lesions and therapy are preserved but not presented here.

#### ACKNOWLEDGEMENT

The writer wishes to thank Dr R. Wasito, Director of the Institute for permission to carry out the investigations, and Professor R. Goenawan and Dr R. Sardi, for their kind co-operation. He is also greatly indebted to Dr V. S. Paranjpe for his most valuable criticism and encouragement.

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# Abstracts

**Cutaneous lesions of the different clinical forms of leprosy.** J. TERCENIO DE LAS AGUAS, *Revista de Leprologia, Fontilles*, 1965, 6, 3, p. 263.

The author points out that skin lesions stand out in the symptomatology of leprosy for their constancy and profusion. As there are very different characteristics he describes the distinct lesions of the different forms.

**1 Indeterminate leprosy:** This form has a special importance in spite of its benignity and lack of stability because of the earliness of the lesions. They are flat macular lesions without being raised above the level of the skin and can easily undergo a papular change or evolve towards a polar form. The coloration of these macules may be either too much or too little and become erythematous or erythematous on lessened colour. They think that the hypochromic are the earliest, occurring in children and often called 'white macules'. They never attain to the colour density of the macules of vitiligo. The most frequent site of these pale macules is in the buttocks, shoulders, face, front of the chest, deltoid region and face, perhaps because in the infant these zones are more intimately in contact with the mother who has leprosy. The size is variable from a lenticular scattering to a wide plaque. The border is practically never well defined and almost always hazy, though sometimes well defined lesions have been noted, and a geographic border. The lesions are usually regular.

In lesions which are both erythematous and hypochromic, the features are combined without large variations. The lesions are modified by treatment and even may disappear spontaneously. When they evolve to a polar type the erythema may accentuate, papules and infiltration may occur, and a histological study may be necessary to find out whether the evolution is lepromatous or tuberculoid.

Mostly indeterminate lesions are associated with benignity and good evolution under treatment. Anaesthesia can be present but bacilli are scanty.

**2 Lepromatous leprosy** without doubt is the most polymorph type. It has macules with a diffuse hazy outline which blends with the surrounding skin. The lesions have a rosy form sometimes like roseola: erythematous and pigmented macules are also common, with brownish-yellow tint, even violet. Less often hypochromic macules exist, with aspect recalling the indeterminate but already having a thicker lepromatous texture.

Apart from the diffusion of the border, all these lepromatous macules are characterized by infiltration and are located in the buttocks, the trunk, the thighs, the arms, cheeks, maxillary border, and forehead. The author has noted some lepromatous patients with macular lesions and infiltrations, which showed a more definite outline and even resembled figured tuberculoid leprides.

Leproma constitutes the typical lesion of this clinical form. The lesions are dermo-hypodermic nodules which almost always are raised above the surrounding skin, the

covering skin being erythematous and pigmented or violaceous, sensitivity is altered, and there is a great richness in bacilli.

The localization is distal in preference, as in all leprosy lesions noted by the author, as Latapí comments 'as if there is a preference for light', so that the zones most affected are the face and limbs. In the face he has noted a preference for the superciliary and frontal regions, cheeks, nasal and maxillary borders, auricular pavilions, and all the nodules tend to fuse, forming leonine and choleric aspects, with a strong background of infiltrative fusion. Although not often the author has noted them in the hairy scalp, in the occipital and temporal zones as much as the neck.

In the upper limb the preference is for the forearm, the lower part of the arm, and the dorsum of the fingers and hand. In the arm these lesions are symmetrical, in the medial and lower aspect, sometimes forming plaques and lepromata covered over with very pigmented skin. In the forearm they are met with in isolated form in the anterior surface and in the lower third of the lateral aspect as a sheet. In the hands, in the dorsum, and the wrist region they occur preferably and less so in the fingers. They occur seldom in the palmar aspect.

In the trunk they especially occur in the scapular regions, the front costal plane, the abdominal and gluteal regions, where they are often hypodermic and need palpation.

In the lower limb they are especially frequent on the medial face of the thighs, knees, and legs, being exceptional in the plantar regions.

In the palate cavity we have encountered lepromata in the palate vault, in the anterior pillars of the fauces and more often in the tongue. These lesions are noted in very advanced lepromatous patients with predominance of nodules, but lesions are often noted in the skin of scrotum, penis, and glans. The size of the lepromata is very variable, from a pinhead to a dove's egg, and the covering skin is erythematous-brownish or coppery in colour, becoming more pigmented when they regress because of the specific therapy.

The leproma can undergo changes. One of these is cure. It begins to lose turgidity, to diminish in size, the covering skin begins to look like an empty sac, folding and umbilicating and disappearing as a nodule, leaving a pigmented scar which is depressible and covered by atrophic skin. At other times the leproma ulcerates centrally and exudes purulent and sanguineous fluid which forms a scale in the form of a plug in the centre. This phenomenon, which results in the partial or total disappearance of the nodule, may result from vascular phenomena in a reactional period in quiescent phases when the leproma grows and does not sufficient circulation, for it is not a very vascularized lesion.

When sheet or plaque lepromata re-absorb they are replaced by zones of great cutaneous atrophy which also gives on pinching the sensation of an empty sac.

These changes are seen very well in the lower third of the forearms, in the medial aspect of the thighs, and in the face.

Infiltrations occur very often, and although they appear in most patients along with lepromata and macules, in some they are the only skin lesion of lepromatous leprosy.

Infiltration is a thickening of the skin which seems to be augmented by erythematous pigmentation and often telangiectasis. The skin has a shining oedematous aspect and the skin folds are exaggerated. These lesions also appear preferably in the distal parts and in the face in the frontal and superciliary regions and temporal regions are apt to be associated with alopecia.

The auricular pavilions are the regions most involved, the nodules making them hypertrophied and pendulous, and there are also infiltrations in the regions of chin and cheeks. In advanced infiltrative patients there is a total alopecia of eyebrows along with an infiltration of the whole face, loss of eyelashes, and a collapse of the nose (the oriental Mongolian face of Negro). In the upper limb the hands appear oedematous and infiltrated, the skin shining and devoid of down hair, the tint erythematous and cyanotic recalling the 'hypogenital face' of Marañón and the 'succulent hand' of Marinesco. These hands and equally the face recall to us patients with myxoedema. In the forearm infiltrations present most in the lower third which disappear centripetally. In the trunk in advanced patients the infiltrations have a pasty succulent aspect, together with absence or scarcity of hair.

In the lower limb the infiltrations are preferably constant and typical in the lower third of the leg, where they form a pigmented sleeve with muscular atrophy and dry and broken skin, which is called 'stocking infiltration'. Infiltration also appears in the dorsum of the feet, which are oedematous, hairless, and with dry skin, sometimes with an elephantiasis aspect. In the thighs the infiltrations are less intense and sometimes with livid and marbled cutis. The long duration infiltrative patients, when they are cured, present an aspect of premature ageing because of the destruction of cutaneous elastic fibres, and the muscular and trophic bony lesions in the limbs add a scar tissue.

Ulcers are frequent in the lepromatous form. Specific lepromatous ulcers occur and also mixed ulcers due to trophic and vascular causes and lack of nerve sensitivity. As specific ulcers, apart from those on lepromata, we can cite those occurring in the infiltrations of forearms and leg, mostly in periods of reaction, ulcers with borders cut off at an irregular point, base dirty and purulent, and which cure more slowly than those of the lepromata. In lepra reactions, especially in the papular with blisters, the bursting of the blister gives place to a shallow ulcer which cures rapidly. At other times the ulcer forms after the spontaneous appearance of a blister which seems to follow approximation to a heat point or a minimum traumatism.

Trophic ulcers affect preferably the lower limb. They localize preferably on the lateral aspect of the limbs, the malleolar areas, the dorsum of the foot, the knee, the tibial crest. There are extensive lesions which circumscribe sometimes the whole limb, which have an indented and geographic border, and are raised and atonic surrounded by a pigmented sclerotic and atrophic skin.

The border of most of the cases is sharp-cut and sloping

and undermined, and the base is very deep and irregular, formed by muscular and bony tissue. The evolution of these lesions is long and they respond badly to therapy usually, and when they cure the centre is covered with a mother-of-pearl scar, with separable scales, surrounded by hyperpigmented zones. Relapses are frequent.

Another ulcer is the perforating plantar ulcer, which sites especially on the head of the first metatarsal and also over the other metatarsals. It is common at the extreme edge of the foot and heel, where pressure is greatest. There is another perforating ulcer sited dorsally on the interphalangeal articulations of the digits of foot and hands, where there are repeated micro-traumata. There is a perforating ulcer in the elbow and the knee.

#### **Lesions of anexures:**

**Hair:** This system is constantly involved in lepromatous leprosy. Alopecia of the eyebrows can present in various degrees, from the initial phases of depilation up to patients with total madarosis in advanced stages. Areas of the beard may have alopecia, especially pre-auricular, maxillary angle chin, and it is typical for the hair of the beard to persist in areas which run from the labial commissures to the maxillary border, giving the 'Chinese moustache' aspect.

Also frequent in advanced lepromatous are forms of alopecia of the temple which begin in the zone of the side-whiskers, affecting several centimetres of the hairy scalp and continue as a fringe to the back of the neck. There the alopecia is very characteristic in the lepromatous; the hair disappears and leaves a quite extensive fringe which gives the impression that the patient wears a wig. Rarely there is fronto-parietal alopecia in patients with infiltrations and lepromata of the hairy scalp, and equally in the upper occipital region. Also the eyelashes are diminished or absent in many patients. In the trunk above all in patients who began their disease in infancy and puberty, diminution or absence of hair is noted in the axillae and thorax, and a feminine distribution in the pubis.

In the upper and lower limbs the diminution or absence of hair coincides with the skin areas affected.

**Nail lesions** are frequent in advanced lepromatous patients, who show skin lesions round the nails.

In patients with advanced neural lesions there is destruction of the nails but mainly they persist in atrophied form, diminished in size and deformed in fingers which have suffered absorption of bones and soft parts.

**Trophic lesions:** These present in the advanced lepromatous patient as a sequel of paralysis and destruction of the nerve filaments. There is sclerotic and atrophic skin, ichthyosis, fissuring, leprotic pemphigus, dyschromia, shining skin, acrocyanosis, oedema, elephantiasis, whitlows, etc.

**Reactional lesions:** In the acute episodes of lepra reactions there is a series of new acute cutaneous lesions. *Nodose erythema* is without doubt the most frequent reactional lesion. Erythematous nodes are disseminated mostly on the extremities. Sometimes they form real plaques. When they regress they lose their coloration and turgidity.

*Polymorph erythema* is also met with in some reactions, when as a single lesion or many or others combined with elements of *nodose erythema*, or large papules with elevated border and blister in the centre. There is a preference for the face in the superciliary and malar regions, and they occur very often in the neck and in the arms and thighs.

*Necrotizing erythema* or the *Lucio phenomenon* is the reactional cutaneous lesion of the diffuse lepromatous form of Lucio and Alvarado, frequent in Mexico and studied by the school of Latapi. It consists of multiple red and painful spots, which become necrotic in the centre after the appearance of a blister. There also exist some skin lesions which are non-specific erysipeloid acute reactions appearing as repeated erysipelas in burnt-out lepromatous patients in whom there are many portals of entry of infection. Such lesions appear most frequently in the legs and there are oedematous plaques complicated with blisters and ulcers, lymphangitis and adenopathy. They respond well to antibiotic therapy.

### **Tuberculoid leprosy**

This is a benign form very polymorph in its skin lesions. The lesions can be either quiescent or reactional, the first most frequently.

### **Quiescent lesions**

*Nodular leprides* have been well described by Souza Campos and Souza Lima, as a primitive form which appears in the infantile age. It often evolves towards cure without leaving scarring, does not suffer episodes of reactivation, and maintains its subcutaneous characters throughout its whole evolution. Souza Campos and Souza Lima have never seen in minors of three years any other clinical form than the nodular tuberculoid lepride.

These lesions vary in size from 2 or 3 mm to several cm and adopt the aspect of rounded tubercles of rosy aspect or brownish erythema, with smooth shiny surface, localized chiefly on the thighs, forearms, and arms, usually bacterially negative. The prognosis is good; there is a tendency to spontaneous cure, reactions do not occur, nor changes to other clinical forms.

*Macular leprides* are less common and contain the typical figured leprides and the atypical leprides. The former have a well-defined border, are papulous, are raised and scale. The colour is erythematous or erythematous with a brownish or violet tint and there is a central zone which is much lighter, hypochromic, or atrophic. These lesions are mostly oval and assymmetrically placed. The border is dentate and geographic and the long axis may measure 10 to 15 cm.

Characteristically, growth takes place at the external border and the lesion in this phase a violet or vinous colour and the surrounding skin presents an absence of histological lesions while the central part inside the delimiting border spreads to the centre of the lesion.

More extensive macular leprides occur, not so oval, of a uniform rosy erythematous colour but not so well marked nor with a contrasting central hypochromia as in other leprides. These lesions are located preferably in the buttocks, trunk, shoulders, front aspect of the forearms, thighs, and face. We have sometimes noted them in palms and soles and the hairy scalp.

When these lesions regress the colour of the border and centre diminishes, the micropapules of the limit diminish, and a fine desquamation begins and goes on to total regression. Reaction of these lesions is rare.

*Atypical leprides*: Macular achromic lesions are rare, or erythematous-hypochromic and erythematous, similar to those of indeterminate leprosy, except that they have a tuberculoid histology, being transformation forms and localized preferably in the buttocks and shoulder.

The benign evolution of tuberculoid leprosy can in certain cases suffer failures in the immune equilibrium, giving place to reactions in the cutaneous lesions and general symptoms. This acuteness of tuberculoid leprosy is sometimes retarded, without bacterial modifications nor immunity changes, which is why it is called 'tuberculoid leprotic reaction'. In other cases the skin picture reacts more intensely, with bacterial and immunity changes, and the form is called 'reactional tuberculoid'. In the 'tuberculoid leprotic reaction' the leprides undergo an increase of colouration in their border, a greater neatness, a greater elevation, but the Mitsuda continues positive and the bacilli negative.

In the 'reactional tuberculoid' the characteristic basic forms of tuberculoid leprosy are modified, at least transitorially, by certain breakdowns in the immuno-allergic state. There are new outbreaks of skin lesions and general changes in the bacteria, such as appearance of single bacilli and globi and negative Mitsuda. These reactional phases can follow each other or this immuno-allergic disequilibrium can change the process of evolution and cause mutation to the lepromatous form.

The change in skin lesions is to increase the colour of the border, which becomes violet or vinous, the whole lesion more raised, broad and hazy, even the centre of the macule elevates and increases in colour and the lesion becomes greater. Outbreaks of new lesions occur, especially nodular and with raised plaques, in colour lively erythematous or violaceous. At other times the leprides flow together forming capricious pictures with shagreen border. Ulceration of these lesions is rare.

Regression follows the general rule of diminution, of elevation of the lepride, laminar scaling of the border, and atrophy, and take on a sarcoid aspect. In parallel the skin picture regresses, the bacilli become negative and the Mitsuda positive.

### **Intermediary leprosy**

This form also called 'borderline', 'dimorphous', 'bipolar', 'fronteriza', 'limitante', constitutes in the author's opinion an intermediary form between the two polar groups in which we include all the atypical and unstable forms, which are mostly reactional tuberculoid which in their mutation towards lepromatous or simply by their reactional characteristics, present skin lesions which do not fit in well into the polar forms and offer atypical characteristics of lepromatous and tuberculoid.

Therefore the lesions differ very little or exactly coincide with those described under reactional tuberculoid leprosy. The author presents figures which illustrate well the clinical features of the conditions he describes.

**Clinical and Serological Profiles in Leprosy**, L. J. MATHEWS and J. R. TRAUTMAN, *Lancet*, 6th November, 1965, p.9p. 15-918.

This was a paper presented to the meeting of the Public Health Service Clinical Society, Staten Island, New York, on 6th May, 1965.

The authors state that numerous clinical and serological similarities exist between lepromatous and dimorphous leprosy and collagenous diseases, such as particularly lupus erythematosus and rheumatoid arthritis. The clinical features include spontaneous skin ulcers, ischaemic necrosis, petechial and purpuric eruptions, vesicle and bulla formation, subcutaneous nodules, enlargement of the liver, migratory arthralgia and polyarthritis, bizarre skin lesions including butterfly facial rashes, and a general tendency towards exacerbations and remissions. Blood findings include anaemia and the occasional appearance of lupus cells. Positive serum findings include rheumatoid factors, circulating thyroglobulin antibodies, false positive serological tests for syphilis, and (consistently) cold precipitable proteins.

Because of these similarities the authors think that leprosy is a disease which should be thought of as a model for the study of states of haemoglobulinaemia, especially the collagen diseases. It is important that the causal agent of leprosy is known, unlike other diseases in the group.

**Role of Plastic Reconstructive Surgery in Leprosy**, by S. C. ALMAST, Leprosy Plastic Reconstructive Surgery Centre, Anandgram, Shahdara, Delhi, *J. India Med. Assoc.*, **45**, 6, 16th September, 1965, pp. 300-316.

The author groups the deformities and surgical complications of leprosy under face, upper extremity, lower extremity, and miscellaneous, and after discussion of their importance in the diagnosis and prognosis of the disease and their consequent public health importance, lists the available plastic and reconstructive procedures. Rhinoplasty and reconstruction of the nose may be by post nasal inlay skin graft, or bone graft, or total reconstruction for total loss. For lagophthalmos there is the operation of temporalis musculo-facial sling. Ectropion can be dealt with by McLaughlin lateral tarsorrhaphy, and/or epiphora by upper to lower lid rotation flap. Loss of eyebrows can be dealt with by grafting of hairy skin, either a free graft, or a transposition flap, or a temporal artery island scalp flap. The ear lobule can be reconstructed, and a face lift operation done for improving aged appearance. Foot drop needs the tibialis posterior transfer operation. The Webster operation is available for gynecomastia. Chronic ulcers and flexion contractures may need skin grafting. There are miscellaneous operations of the bones, joints, and nerves. Many practical details are given and the author explains the necessity of trained physiotherapy. He mentions the scarcity of scar or keloid formation.