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CONTENTS.

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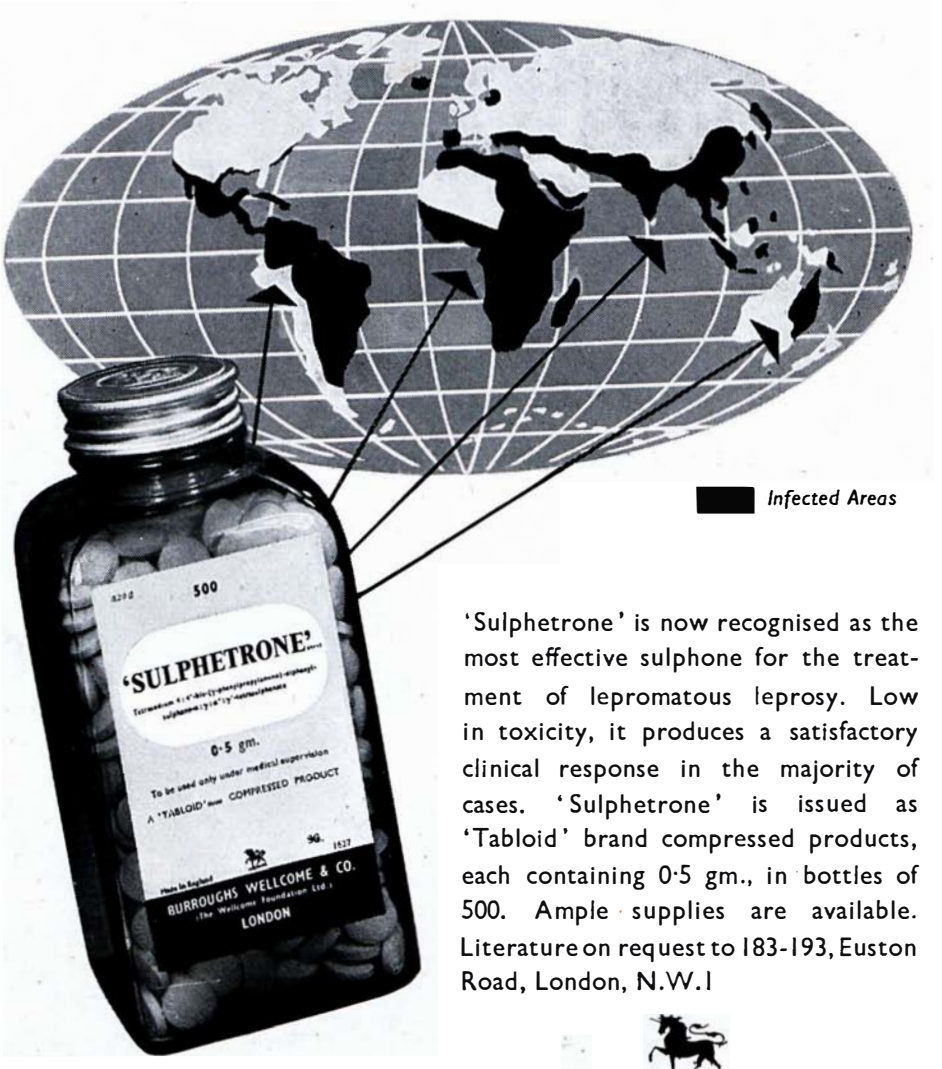
IN THE **FOREFRONT**



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EDITORIAL

In this issue we welcome the first fruits of two new projects of the British Empire Leprosy Relief Association.

In Dr. Cochrane's "Practical Textbook of Leprosy" the following sentence occurs:—"The number of hospitals or sanatoria dealing with leprosy which can boast of a department devoted to work of this kind (physiotherapy) is comparatively small, despite the prevalence of neural involvement in leprosy".

Dr. Cochrane would be the first to agree that this statement is a conservative one. His short account of physiotherapy is the only one in any English textbook on leprosy. The prevention and restoration of trophic changes in leprosy should be an integral part of treatment in every leprosy institution. The insistence on physiotherapeutic treatment in every case of nerve leprosy meets all too frequently with apathy and lack of enthusiasm on the part of leprosy workers and patients alike. We are therefore particularly glad to introduce Mr. S. Alderson's able and practical observations in this field.

The British Empire Leprosy Relief Association has also sponsored a Leprosy Research Unit in Nigeria, with Dr. John Lowe as its director. Dr. Lowe's preliminary views on sulphone research are given in this issue. This represents the first of a series of reports on modern research from an authoritative source consisting of a highly qualified team of workers.

The important and difficult question of type mutability in leprosy is discussed by a number of authors in this issue. The subject is of primary importance. Among Chinese in Malaya cases of leprosy normally start clinically and histologically as pure tuberculoid. Again in the normal course of events they degenerate into lepromatous cases. This is not a matter of opinion but of proven fact. In other parts of the world a careful study of the early history of lepromatous cases reveals presumptive evidence of a tuberculoid onset. Again, in many lepromatous cases physical evidence can be found suggestive of a previous tuberculoid condition. There can be few leprologists who have not heard the statement from a lepromatous case "At first the doctor said it was ringworm"—again presumptive evidence of a primary tuberculoid phase.

There is thus both factual and presumptive proof of the mutability of tuberculoid into lepromatous leprosy. We are immediately faced with the paradox that able and experienced workers like Lowe, Cochrane and Fernandez have not in their

vast experience observed such a change to be common or even possible. Differences in the interpretation of the histology or clinical appearance of tuberculoid leprosy do not account for this apparent contradiction.

Let us assume, therefore, that there are significant type variations both in neural tuberculoid and lepromatous leprosy. We should then have in neural tuberculoid leprosy (1) the non-anaesthetic depigmented macule peculiar to Nigeria; (2) the immutable tuberculoid of Cochrane and Lowe; (3) the Malayan tuberculoid, with its progress to lepromatous change; (4) the type where both lepromatous and tuberculoid lesions appear at the same time on separate parts of the body; (5) the mixed type with a combination of tuberculoid and lepromatous leprosy. Equal differences could be made in lepromatous leprosy. There is, for instance, a marked clinical and prognostic difference between the mild and indolent lepromatous leprosy seen in Nigeria and certain parts of India; as compared with the virulent and eruptive form of the disease seen in Malaya. Further development along these lines can only lead to hopeless confusion in classification.

Aristotle has said that the only insoluble problem is the problem in which the premises are incorrect. If so, the symposium in this issue would seem to call for a basic reorientation of our ideas on the classification of leprosy.

PHYSICAL THERAPY IN LEPROSY

S. ALDERSON

It is considered by the British Empire Leprosy Relief Association that physical medicine in the form of physiot
and occupational therapy has an important part to play in the treatment of leprosy.

In assessing the value of physical treatment the economic aspect of these disabilities must be taken into account. Large numbers of patients throughout the world are manual workers. Advanced stages of main-en-griffe, especially if accompanied by fore-shortening of the fingers make the use of implements and tools extremely difficult, and in many cases quite impossible. This can

obviously lead to hardship both when the patient is in the settlement and after he has been discharged. Although arrangements can be made in some settlements for help to be given to crippled patients it is doubtful if it is, or can be, offered to all. Outside the settlement it is very often the case that the cripple is looked upon as a useless member of the community and left to his own quite inadequate resources. Some patients even prefer to stay in the settlement after discharge, having this fact in mind.

The psychological outlook is also of major importance. It is disturbing to the patient to feel that, although he is experiencing general improvement yet the disability of his hand or foot or both is increasing. This leads to the apparent anomaly of a patient entering a settlement with a whole body and leaving it symptom free with physical deformities of the limbs. Confidence in the general treatment is not encouraged under these circumstances.

Our aim is, therefore, to remedy as far as possible the existing cases of muscular atrophy and contractures and, in the case of patients complaining of painful and enlarged nerves, to prevent the consequent trophic changes.

In order to confirm the necessity for physical treatment, a survey of contractures was carried out among patients at a number of Nigerian settlements. This survey was of a reconnaissance type, and covered all kinds of contractures. Dupuytren's contracture is common in Nigeria, probably being exacerbated by the extensive use of machetes, and on the coast in the Creeks Area, by the use of canoe paddles. Yaws is, of course, widespread and leaves behind many deformed hands. Taking all non-leprotic contractures into account, however, the number of leprotic contractures is very high.

A further survey was carried out at the Uzuakoli settlement. This included all stages of main-en-griffe. The survey was made in considerable detail and dealt specifically with the ulnar nerve. Examination was made for pain, nerve enlargement, muscular atrophy, contracture and foreshortening of the fingers. This survey brought a number of interesting points to light. The number of potential cases is as great, in fact slightly greater, than the number of cases where trophic changes are evident. This is especially so in the case of the children where 74 out of 101 affected cases showed trophic changes. Of the 378 affected cases 11% had their left arm only affected, 25% their right arm only, and 65% both arms affected.

Dr. Ross undertook a survey of 194 patients. Of these 50 (26%) showed signs of nerve involvement with slight wasting and involvement of muscles and eminences; 24 (12%) showed marked

signs of wasting with contracture; 13 (7%) showed an advanced stage of wasting of all muscles of the hand and contracture. This gives a total of 45% affected of cases examined. It is again evident that the early cases are in the majority.

It proved difficult to find an occupation having a remedial value for main-en-griffe; one which, having in mind the patient's lack of co-operation, definitely necessitated the use of the little, ring, and middle fingers. The only type of equipment which seemed to offer itself was a hand-operated table loom based on a Dryad design modified by Miss McCaul, M.A.O.T. of the London Hospital. This had been used to encourage flexion of fingers and wrist, and to increase hand-grip. A number of these looms were made. Their operation was carried out by the turning of cylindrical wooden handles about 6" long. These were detachable and of varying diameters. For leprotic contractures the handles were reversed in order of use, progressively larger handles being used. A range of eight sizes was kept, from 1" to $2\frac{3}{4}$" diameter in $\frac{1}{4}$" increases.

Each patient's hand was "fitted" individually, the largest handle that a patient could comfortably use being given first. Each patient was re-examined at intervals, and the next largest size given if warranted. These looms were used over a period of seven months, and produced very satisfactory results. They had drawbacks, however. Although they experienced a certain initial popularity, this soon waned. The popularity was due to the fact that knowledge of weaving on a European loom was considered to be of potential economic value. Also, there seemed a possibility that the material woven, 2" bandages, might become the patient's own upon its completion. When the novelty wore off, and the latter possibility failed to materialise the popularity waned.

The five principal exercises adopted were:—

(1) Fingers of one hand interlocking with those of the other, palms facing away from the body, arms bent at the elbows. Exercise by straightening arms. The fingers are thus forcibly extended against the back of the opposite hand.

(2) Forearms horizontal against the body, palms of hands touching, both hands vertical. Exercise by abducting all the fingers fully and then pressing opposite numbers and abducting the fingers so that all fingers and thumb tips close in to touch each other, at the same time allowing arms to be separated.

(3) Hand placed palm upwards on the table. Exercise by

stretching and flexing fingers by touching the ball of the thumb with each finger tip in turn.

(4) Same position. Exercise by touching each finger tip with the thumb, seeing that the fingers do not move.

(5) Making a cup out of the palm of the hand with the finger tips close together and the knuckles slightly bent. Exercise by bringing the little finger in front of the others.

Two exercises with simple apparatus were found most satisfactory. One was carried out with a flat stick about 3′ 6″ long, issued to each patient. On one side, marks were made showing the position of each finger when they were all fully abducted, care being taken that the hand was held flat. On the other side similar marks were made with the hand held vertically down over the stick and the fingers " walking " along it. The marks were made on the first day of treatment making sure that there was no strain. This also served as a guide to improvement.

The other was designed to give resistance to flexion of the fingers. It consisted of a flat rectangular piece of wood with a semi-circular inset to receive the ends of the fingers and so prevent slipping. Two strings were attached to the wood and from these hung a container partially filled with sand. The forearm was placed in the supine position upon the table, the finger tips overhanging. The rectangle was placed upon the ends of the fingers and the fingers flexed against the weight of the suspended sand. The latter could be varied in quantity to vary the degree of resistance as required.

Heat treatment took the form of baths of paraffin wax and, alternatively, hydnocarpus oil. The only paraffin wax available had a very high melting point and even when mixed with liquid paraffin a temperature of 120°C was required. This created no difficulty but wasted time. It took a considerable time to cool down to 100°-105°C because of the high atmospheric temperature. In application it proved quite satisfactory. The draw-back was that children always broke the wax " glove " at the wrist if triple immersion was adopted, because large deep containers were not available and basins had to be used with larger basins to hold the water jacket. Ladling was tried but there never seemed to be enough wax on the inside of the " glove." These faults could be overcome with adequate equipment.

The oil bath on the other hand was very much simpler and for this reason alone might be considered preferable. Using a pressure stove (primus type) it took only a few minutes to bring the temperature up to 100°C, at which it could be used directly.

The saving of time was considerable and the hydnocarpus oil acted as an excellent lubricant for the massage which followed. The oil bath was used for the most part and wax only for those patients who were prepared to take more time on their treatment, and for patients whose fingers, although not necessarily contracted, were stiff and lacking in normal function.

Massage was given for periods of from five to fifteen minutes immediately following heat treatment. This consisted of effleurage, kneading and friction. The effleurage, was given to the whole of the hand and, later, to the forearm along the ulnar border. Finger kneading was given to all the muscles of the ulnar distribution in the hand, especially the interossei and the hypothenar eminence. Friction was given to all the fingers.

The introduction of these forms of treatment took a few months. By this time it became evident that the treatment given should be standardised. This made the work easier for the staff to carry out, especially when working with a "class" of children and adults at the same time. Thus a standard treatment was introduced which consisted of heat treatment followed by active finger exercises. In the case of a class consisting of, say, six or more children the loom proved useful as a "filler" between the massage and exercises. As at this time there were two patient-assistants it was possible to massage only two patients at one time. Therefore, the drill was for two to be oil-bathing their hands, two being massaged, whilst the rest operated looms either waiting to receive this treatment, or, having received it, waiting for the others to finish. When all had been given the heat treatment and massage one assistant called them together and took them in the active exercises, finishing with the "stick" exercises, If any time remained they were put back on to the looms. Adults were treated individually.

Each new case was given a thorough examination by the European in charge, the results being recorded on a printed case sheet. Tests were made for anæsthesia to light touch, pain and thermal sensation muscles of the hand were tested for weakness; note was made of trophic changes and pain. Personal details were noted. Type of remedial treatment was specified and entered with dates; daily attendance was recorded on the reverse side. The assistant was then given the treatment instructions which he noted in his treatment book, one page was kept for each patient and daily attendances were recorded.

Occupational therapy in the form of the hand loom described was efficacious. The principal drawback was its lack of popularity with adult patients, especially the men. Children could be made

to use the looms, women could be induced to do so, but the men, for the main part, objected. This type of treatment in particular requires full co-operation with the patient in order to be of any great benefit. Its full range of movement was not sufficient by itself and it cost time to set up the looms after each woven bandage was completed. The looms were quite simple and inexpensive to construct, the bandages made proved superior to manufactured ones when applied to ulcerated feet.

The following case sheets demonstrated results achieved.

Case A.

A boy of 16 years. Admitted to settlement in 1945. Date of onset of disease was 1937. Date of onset of disability was 1945. Disability: Severe main-en-griffe of left hand, nerves affected; the ulnar was slightly enlarged; muscle weakness; all flexors very weak; almost complete loss of function of interossei. Contracture: Moderate over fifth, fourth, and third fingers. Atrophy and severe wasting of all interossei and the two eminences; metacarpals prominent on both aspects. Pain: None. Physical condition: Good generally, prognosis was good. Attendance: Good, but treatment was missed for a period of nearly three months due to school holidays and an extended visit home.

The treatment commenced in October, 1947. Very favourable reaction was shown in abduction and especially in flexion. The fingers became more flexible and considerable strength was developed in the flexors, the contracture was obviously reduced.

Later on more attention was paid to the interessei, and more abduction exercises were carried out.

At this time, May, 1948, a record was made of the hand with the fingers fully abducted. Six weeks later a check was made for increased abduction. This was found to be $\frac{1}{2}$" over the four fingers and 1" between the thumb and index finger. Over the same period the degree of contracture was recorded also. The distance was measured from a flat surface to the underneath side of each finger at the proximal inter-phalangeal joint. In this length of time the distance had been reduced by 1/10" for each finger. The patient was pleased with the progress and became increasingly co-operative.

Case B.

A woman aged 45 years. Date of onset of disability 1946(?). Type of disability: Main-en-griffe of both hands, the left hand

was more severe than the right. [Only the left hand will be described here.] Nerve affected: the ulnar was greatly enlarged for 4" above the elbow. Muscle weakness: considerable in flexors, power of extension very weak. Power of abduction and adduction of second finger was slight, with that of fourth almost absent, and that of fifth completely absent. Contracture: Considerable in the fifth, fourth, third, and second fingers. Atrophy: Both eminences and the interossei showed wasting. Pain experienced in ulnar nerve, particularly in the upper arm. Physical condition: Moderately good. Treatment commenced: 10/11/47 and was continuous.

It proved very satisfactory, the pain was alleviated progressively, the range of movement increased and general mobility of the hand and arm improved. Records of progress were kept over six weeks and showed an increase in adduction.

Exercises, based on a monograph by Dr. Ryrie, were introduced into the school curriculum at one of the settlements. Exercises chosen for their remedial and preventive value for both arms and legs were carried out in the P.T. and games period, and finger exercises were carried out in the class rooms between periods. These proved successful and should be carried out in all settlements.

Regarding staff it was found that satisfactory assistants could be found amongst the patients. It proved fairly simple to teach them the elements of the work and they learned quickly.

The figures of the three surveys proved beyond doubt the necessity for the introduction of physical treatment both in its remedial and preventive forms. This applies especially to children where the number of cases showing involvement of the ulnar nerve only, is two to three times greater than those cases showing trophic changes.

In spite of the comparatively short duration of the experimental work and its improvised nature, the results obtained prove the possibility of introducing physical therapy successfully into leprosy settlements.

A physical treatment centre provides no great obstacle. African assistants can be found from among the patients and, although the inception of a centre requires a good deal of time and work on the part of a European, the routine work of an established centre can be included with that of a Welfare Officer. The

cost of establishing a centre is small, the main item being the provision of Primus stoves and large basins or containers for wax and oil. Even if occupational therapy is introduced the cost of making the looms described is comparatively small. Running expenses consist of little more than the salaries of African assistants. If these are colony patients then the amount is very small.

Classification of cases was discussed with Dr. Ross at considerable length, having in mind the parts which physical treatment and operative surgery might play in ulnar nerve involvement and consequent disabilities. Those which suggested themselves were:

Early Stage

(a) Cases with enlarged and acutely painful nerve, but with no physical signs. If the patient has acute neuritis with loss of function of the hand, the case requires primarily injection therapy or operative surgery.

(b) Cases with enlarged but not acutely painful nerves. Physical treatment should be tried for this type of case. If disability or loss of function becomes evident in spite of physical treatment then operative methods should be considered.

(c) Cases with neuritis and slight signs of muscular atrophy. If neuritis is slight and the nerve is generally enlarged longitudinally, physical treatment should be tried, but if the nerve is enlarged, bulbous, tense and tender, operative methods should be considered.

Advanced Stages

Pain is less a feature in these cases than in those of the early stages and physical signs are more marked. The nerve is fibrous but not necessarily tender; atrophy and contracture are present. Physical treatment should be given in these cases.

Post-Operative Cases

These should all be given physical treatment.

It is hoped that this report will prove the desirability and the necessity for physical medicine and offer a basis upon which treatment might be generally established.

SURVEYS

SURVEY OF CONTRACTURES.

OJI RIVER SETTLEMENT.

Type of Case	*Men*	*Women*	*Children*	*Total*
Early Cases	44	19	36	99
Advanced Cases	54	18	35	107
Total Affected	98	37	71	206
Total Examined	218	131	285	634
% Affected	**45**	**28**	**25**	**32**

OSSIMO SETTLEMENT.

Type of Case	*Men*	*Women*	*Children*	*Total*
Early Cases	67	17	32	116
Advanced Cases	136	15	30	181
Total Affected	203	32	62	297
Total Examined	322	84	200	606
% Affected	**67**	**38**	**31**	**49**

ITU SETTLEMENT.

Type of Case	*Men*	*Women*	*Children*	*Total*
Early Cases	325	148	138	611
Advanced Cases	338	156	94	588
Total Affected	663	304	232	1199
Total Examined	1075	507	550	2132
% Affected	**61**	**60**	**42**	**56**

UZUAKOLI SETTLEMENT.

These figures given exclude those patients (a) aged over 50 years, (b) with eight fingers severely contracted, (c) with six or more fingers badly contracted and more than two foreshortened, (d) post-operative cases. These patients numbered, possibly, 10 to 15% of the cases noted; this would make the total number of affected patients approximately 200, or 16% of the patients examined.

Type of Case	*Men*	*Women*	*Children*	*Total*
Early Cases	26	32	15	73
Advanced Cases	57	30	7	94
Total Affected	83	62	22	167

Early cases = Contracture of two fingers or less.
Advanced cases = Contracture of more than two fingers.

SURVEYS (Continued)

DETAILED SURVEY OF MAIN-EN-GRIFFE AND NERVE INVOLVEMENT.

(UZUAKOLI)

Type of Case	*Men*	*Women*	*Children*	*Total*	
Pain only	3	12	3	18)	190
Enl. Nerve	32	7	26	65)	"Potential"
P. + Enl. Nerve ...	32	30	45	107)	Cases
P. + E.N. + Atrophy or Contracture	13	13	8	34)	188
(P) E.N. + A + C ...	21	20	7	48)	Cases
(P) E.N. + A + C + Foreshortening	13	6	6	25)	showing trophic
A. or C.	10	12	1	23)	changes.
Other Combinations	27	23	5	55)	
Total Affected ...	151	126	101	378	
Total Examined ...	280	203	195	678	
% Affected	**54**	**62**	**52**	**56**	

NOTE: Both arms were examined in the case of each patient. As previously stated, two-thirds of the total number affected were bi-lateral cases, but for the purpose of the survey only one could be quoted. It was decided to quote the arm most severely affected. Therefore the figures given for "potential" cases are conservative.

SULPHONE TREATMENT OF LEPROSY

JOHN LOWE

Sulphone therapy of leprosy has n
years in certain centres; almost all reports on results of treatment are favourable (Refs. 1 to 15).

There are one or two factors which from a theoretical standpoint might favour chemotherapy of leprosy. First, there is the

fact that leprosy is a very chronic infection in which the vital organs of the body are practically unaffected either by the bacilli themselves directly or by toxins produced by bacilli; therefore, the chemotherapy of leprosy does not, as in other diseases, involve a race against time and an attempt to get the infection under control within a limited period before irreparable damage is done. Secondly, there are strong indications of considerable immunity to leprosy in human beings; for example, the difficulty with which the disease is transmitted even by experimental inoculation, and the slowness with which the disease develops, even in the severe lepromatous case. These two factors might mean that a chemotherapeutic agent which affected the vitality of the organisms only slightly might still possibly just turn the balance and enable the body to combat and overcome the infection in the long period of time available.

SULPHONE THERAPY IN PRACTICE.

When sulphones were first studied and were found to be active against the tubercle bacillus not only *in vitro* but, to some extent, in the guinea pig, the chances of chemotherapy of leprosy seemed better; but when sulphones were found to exert little influence on tuberculosis in man, the chances again seemed to recede.

But there were those in the United States who were not prevented by the theoretical difficulties outlined above from making the trial of these drugs in leprosy, a long and difficult trial; gradually it appeared that good results were being seen, and as more work is being done the reported results appear to be improving. Although the treatment has now been used for several years in a few centres, the initial wave of optimism has not yet been replaced by a trough of depression; nor do we think that this is likely as long as scientific caution is used in reporting results of treatment.

These remarks must not be read as indicating that the problem of leprosy treatment has been solved. The sulphone treatment has grave limitations; it is dear; it has to be given for periods varying perhaps from two years upwards, and its ultimate results are not yet clear. Its value in the non-lepromatous forms of the disease has not been demonstrated; in fact it is reported to be of no value in such cases. The writer, however, having had over twenty years' experience of leprosy and its treatment with other remedies, and having now had some experience of sulphone treatment, feels that a very definite advance has been made. His practical and personal experience of sulphone treatment is confined to the last eight months and covers less than 200 cases,

mainly lepromatous. The results are obtained in the more severe infectious progressive lepromatous forms of the disease, which have been least amenable to other forms of treatment, and which present the great problem in treatment. Further, the treatment can be given orally and in ambulant patients and, contrary to some reports, it is found to be well tolerated, toxic effects being few and usually not serious. The beneficial effects are seen in varying degree in almost every lepromatous case treated for a period of six months or more, the improvement being both clinical and bacteriological.

MODE OF ACTION OF SULPHONES.

The question arises, how do the sulphones act in leprosy? The sulphones were selected for use in leprosy because of their action on acid-fast bacilli *in vitro* and in experimental animals; surely it is unnecessary to advance quite a different explanation of their activity in leprosy in man. There seems no adequate reason to doubt that the action in leprosy is on the bacilli; the dimunition in the number of bacilli and the change in morphology of the bacilli seen in cases under prolonged sulphone treatment can be very striking. It is, however, not clear whether the action is bacteriocidal or merely bacteriostatic.

But it may be asked " If the action is a direct one on the bacilli, how can the bacilli (or at any rate acid-fast material in more or less bacillary form) persist for years during sulphone treatment, even if in steadily diminishing numbers? "

To this question there appear to be two possible answers. Few workers who have not made a special study of the matter realise the fantastically large numbers of bacilli present in leprous lesions in a lepromatous case, and the extraordinary way in which even dead lepra bacilli can persist in the body in acid-fast bacillary form. The enormous numbers of bacilli in lesions is shown by a microscopic study of sections of leprous nodules properly stained to show bacilli, and also from the study of bacillary counts in emulsions made by grinding up leprous nodules of known size. Hanks (Ref. 18) has shown that nodules may frequently contain more than an American billion (one thousand millions) of bacilli per cubic centimetre. The long persistence of even dead bacilli in living tissue is shown by a study of animals injected with killed lepra bacilli, or by making smears from the skin at the site of intradermal injections of lepromin in a healthy person who has been lepromin tested, i.e., who has had injected into the dermis about one million dead bacilli; bacilli may be recovered over periods up to one year and even more.

A consideration of these facts shows that there is nothing surprising about the long persistence of acid-fast bacilli in lepromatous cases treated with sulphones, bacilli persisting long after clinical activity of the disease has subsided. It is not impossible that these persisting bacilli are dead, although this cannot be proved.

For the discharge of patients we still have to maintain the criterion of the failure to demonstrate acid-fast bacilli in the tissues examined by the usual methods, but it should be realised that this criterion may be a very harsh one in certain cases. It would be interesting to study patients who, after say two or three years sulphone treatment, have ceased treatment whilst still showing bacilli in the tissues, and to see whether these bacilli slowly disappear in spite of the cessation of treatment.

The second answer to the query regarding the persistence of acid-fast bacilli in sulphone treated cases is concerned with the possibility that the bacilli may become sulphone resistant and thus be enabled to survive and persist though in diminished numbers. If this were the true explanation, a high incidence of relapse would be expected in patients discontinuing sulphone treatment. No one has yet reported such a finding, perhaps because too few patients have, as yet, been treated and then observed for long enough. But the evidence so far available is that, after sulphone treatment, relapse, though not unknown, is not common.

At this point of our consideration of possible modes of action of sulphones, a little speculation might be useful.

> Suppose we had a chemotherapeutic agent so efficient that it would kill off all the bacilli in a lepromatous case in a few days or weeks; what changes could reasonably be expected to follow such treatment in a patient with lepromatous leprosy? Firstly, the dead bacilli would almost certainly persist for many months, if not for years; clinical activity due to the multiplication and dissemination of bacilli in the body would cease rapidly, but symptoms caused merely by the presence of bacilli or by the reaction of the body to the bacillary products liberated by the slow disintegration of the dead bacilli would probably disappear much more slowly. Secondly, we should expect to find no sudden change in the histopathology of the lesions; the active leprous changes would probably slowly be replaced by atrophy and fibrosis, as the dead bacilli slowly disintegrated. Thirdly, we should not expect a rapid change in immunology, the lepromin test giving positive results in cases previously negative. The

results of this test normally show only minor variations in degree and not in kind, with variations in clinical and bacteriological activity in any given case.

In other words, the rapid destruction of all the bacilli in the body by our imagined chemotherapeutic agent of high potency would probably be followed by the same sequence of events, but occurring with greater rapidity, as we now see with sulphone therapy.

The point of this speculation is this; that in the slow subsidence of clinical activity of leprosy under sulphone therapy, in the slow appearance of the acid-fast bacilli from the lesions, there is nothing inconsistent with the view that the action of the sulphones is a direct one on the bacilli.

This is the view of Faget *et al.*, (Ref: 5) who, summarising five years observation of promin therapy, state "the action of promin appeared to be a chemotherapeutic effect on the aetiological agent of leprosy." In the same article, however, they make the following remark, "the important finding is that promin appears to eliminate bacillary infection of the blood vessels and blood stream, thereby preventing the formation of new lesions." This is probably true, but it would appear not to be the whole truth. It cannot explain the subsidence of the lesions present before treatment started. It appears probable that sulphone is taken up by tissue cells, particularly reticulo-endothelium, including the actual cells of the leprous lesions, and that it exercises an influence on the bacilli in the lesions, which are mostly intracellular.

It is worthy of note that the therapeutic effect of sulphones in leprosy can be produced by a dosage and with blood levels which, on theoretical grounds and on evidence gained by studies of tuberculosis in guinea pigs, would appear to be hopelessly inadequate; but this is perhaps another matter in which practical experience is of far more value than theory. There is some evidence that sulphones are concentrated in the leprous lesions.

FACTORS INFLUENCING THE EVALUATION OF SULPHONE THERAPY.

The enthusiasm, or lack of it, with which individual workers have greeted sulphone treatment has varied, and has obviously been influenced by a number of factors. Thus the value attached to sulphone treatment by any physician tends to be influenced by the severity of the leprosy with which he deals (for leprosy varies widely in severity in different countries and peoples), and upon the value he attaches to other forms of treatment, particularly hydnocarpus treatment. For example, in the Leprosarium at

Carville, Louisiana, where sulphone treatment originated, the cases of leprosy are mostly of the severe lepromatous type and hydnocarpus treatment has never given satisfactory results; therefore sulphone treatment is regarded by patients, even more than by physicians, as a great triumph, although Faget and others (Ref. 5) working there have not hesitated to state that "Promin is the best treatment of leprosy ever used there." From India, on the other hand, with leprosy on the whole less severe than in some countries, publications on sulphone treatment have been few and rather lukewarm (Refs: 15, 16, 17). It is, therefore, striking to find among those who write most enthusiastically of sulphone treatment Muir (Refs: 10, 11 and 12) who was for many years perhaps the strongest advocate of hydnocarpus treatment. Muir (Ref: 12) states frankly of diasone, "During more than twenty-seven years of experience of leprosy treatment and the trial of many drugs, the author has not seen any remedy for definite lepromatous cases of leprosy which has given such uniformly favourable results", a striking statement from such a worker, yet one which the present writer, even from his more limited experience of sulphone treatment would support. Reports of other workers from other countries are, so far, few in number, but practically every one is favourable.

A worker's attitude to sulphone treatment will almost certainly be influenced by his views on the evolution of leprosy. For example, a worker who believes that tuberculoid cases commonly become lepromatous, that hydnocarpus treatment can prevent this change, and that sulphones are of no value in tuberculoid cases, will be likely to consider sulphone treatment to be of limited value. The present writer holds none of these beliefs, and tends to think that the value of sulphones in tuberculoid cases has not yet been thoroughly studied with due consideration of what might reasonably be expected from chemotherapy in such cases.

> There is no obvious reason why sulphones (if their action is on the bacilli, as it appears to be), should not be of value in the treatment of all active cases of leprosy irrespective of type. All leprous lesions are caused by bacilli; either by the presence of large numbers of bacilli with little tissue reaction, e.g., in the lepromatous type, or by the reaction, probably allergic in nature, of the tissues to the products of the relatively small number of bacilli, possibly liberated by the destruction of some of them, e.g., in the tuberculoid type. So far, only a few tuberculoid cases have been treated, mostly for limited periods, and results do not appear to be

entirely negative, although the evaluation of any treatment in tuberculoid cases is notoriously difficult because of the marked tendency to spontaneous subsidence.

Without wishing to discuss in any detail the relative merits of sulphone and hydnocarpus treatment, one may mention a few points. The main difference between results of hydnocarpus treatment and sulphone treatment appears to be in the proportion of cases responding. Hydnocarpus treatment can, on occasions, produce marked and progressive improvement in lepromatous cases, probably as impressive as that produced by sulphones, but the proportion of treated cases showing satisfactory improvement is much lower. Cochrane, a strong advocate of hydnocarpus treatment has recently stated (Ref: 17) that " from 30% to 50% of early cases of lepromatous leprosy respond satisfactorily to properly administered hydnocarpus therapy." How can this possibly compare with the response to sulphones seen in almost every lepromatous case treated, whether early or advanced? Muir (Ref: 11) has recently emphasised the constancy of the response to sulphones and others have reported similarly. No more need be said on this point. Cochrane (Ref: 17) also states that the " sulphones are the treatment of choice in advanced lepromatous cases "; this statement might be read (one feels incorrectly) as indicating that he thinks sulphones are less effective in early cases. Faget *et al.*, (Ref: 5) have reported that the best results of sulphone treatment are seen in the early lepromatous cases. Cochrane (Ref: 17) also points out with ample justification that the high cost of sulphones at present makes quite impossible their wide adoption in poor countries, such as India. The same may be said of most of Asia and Africa. This factor is, however, less potent in other countries than in India where, presumably, hydnocarpus oil is obtainable in good quality at a reasonable price. Other countries, such as West Africa, are obtaining from India hydnocarpus oil, often of miserably poor quality, and at no cheap price, and trouble with injections is very common and serious.

Undoubtedly, hydnocarpus treatment will continue to be used for some time yet, but where sulphones are available they should be the treatment of choice in lepromatous cases, if not in others. Some workers will undoubtedly prefer to treat patients with both remedies simultaneously; others will welcome the opportunity of discarding the painful and tedious injection treatment, particularly the intradermal injections which efficient hydnocarpus treatment necessitates.

THE SIGNIFICANCE OF SULPHONE THERAPY.

To the writer's mind a very important fact is this; that for the first time a group of chemotherapeutic agents, not seriously toxic in therapeutic doses, and capable of being given, some of them continuously, for many months on end, has been found to exert a very definite influence upon the bacterial disease, leprosy, which possibly of all bacterial diseases would, on general grounds, be expected to be the least likely to be susceptible to such treatment. The scope of chemotherapy has been extended in quite a new and, to many of us, an unexpected direction. This fact is important, not only to leprosy work, but to other fields of medicine.

One cannot help feeling some satisfaction that leprosy treatment, which has for so long made such slow progress, has now made a definite advance, and further one hopes that other fields of therapeutics may benefit from this advance. Our experience of sulphones in leprosy may help workers studying other chronic infections, particularly acid-fast bacillary infections.

This new development, the sulphone treatment of leprosy, should give very welcome encouragement and stimulus to anti-leprosy work and to individual workers everywhere.

The influence of sulphone treatment on anti-leprosy work is only just beginning to be felt. At the National Leprosarium, Carville, Lousiana, where the treatment started in 1941, the change for the better in the outlook is apparent from the publications of medical staff and also of the patients in the journal which they publish, and from the increase in the discharge rate; one is informed that this optimistic outlook is very apparent to visitors. A similar change will doubtless be seen elsewhere as patients realise that the chances of arresting the lepromatous form of the disease are greatly improved.

How this will affect anti-leprosy work remains to be seen. One may expect increased demands for sulphone treatment and for admission to institutions using it. An increased discharge rate of healed lepromatous cases may be expected, which may necessitate increased staff and facilities for supervision and re-examination of discharged cases. There may be the need for the modification of the types of leprosy institutions and methods of work, since more patients should be effectively treated and discharged, and fewer patients will remain indefinitely, and finally die in leprosy institutions.

Cochrane (Ref: 16) has written rather critically of sulphone therapy, stressing that Indian patients do not tolerate it well, and

also that it may have a harmful effect on prevention by isolation, which he considers more important than treatment. He is almost alone in finding the treatment badly tolerated. One can agree that in the prevention of leprosy the establishment and maintenance of a reasonable degree of isolation of lepromatous cases, particularly from children and young people, is of paramount importance; but the present writer would go further and state his opinion that without a treatment much more effective in lepromatous cases than those used in the past, attempts at isolation of sufficient lepromatous cases of leprosy to influence the spread of leprosy in the general population are, in most countries, greatly handicapped, if not doomed to failure.

To put the matter briefly; usually a person with leprosy will undergo and maintain isolation only if it is accompanied by a treatment sufficiently effective to give him a good chance of the disease being arrested, and the isolation therefore ended, within a reasonable period, a few years at the most. In most countries where leprosy is common, without this inducement of an effective treatment, so many patients will refuse isolation if voluntary, or avoid isolation if compulsory, that the control of leprosy will be impossible. In these circumstances any improvement in treatment is potentially an aid to prevention. It remains to be seen whether sulphone treatment is, or can be made, sufficiently effective to afford this aid to preventive work which is so much needed.

It is true that there are dangers to be guarded against; improved treatment must not be regarded as removing the need for a reasonable degree of isolation; the treatment must be given efficiently and must not cease as soon as clinical activity of the disease disappears, for this might only enable patients to live longer and spread the infection more. The methods to be adopted to avoid these dangers will vary in different countries, but it should not be impossible to devise suitable methods.

To conclude on this point: the writer feels that sulphone treatment wisely used should not hinder preventive work but should aid it.

Finally, there is the effect of this new development on the individual leprosy worker. While knowledge and other aspects of leprosy has steadily increased, until now no fundamental change in treatment has occurred in the last forty years or so, since injection treatment with hydnocarpus oil and its preparations became established. Improvements have been made in the preparations used and in methods of administering them, but the basic idea of the treatment is still the same, and the limitations

of the treatment have long been apparent. Now a definite new development which is full of promise has appeared, and a new field of investigation has been opened up. It is to be hoped that more medical men will be attracted to take up leprosy work, to exploit these new advances to the full, and make further advances.

There is now for the leprosy worker a feeling that gives some satisfaction, that with the sulphones he is using treatment that has a rational basis, even if little is known of the mode of the action. He can feel that here rational and planned research in chemistry, in bacteriology, in experimental animals and finally in human beings has given results even in the disease, leprosy, which often appears so irrational in its behaviour.

We must remember, however, that theorising, however rational, must never replace practical experiment; if it had been allowed to do so, the sulphones might never have been tried in leprosy, because the theoretical difficulties seemed so great.

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LEPROSY IN THE BRITISH WEST INDIES.

E. MUIR.

At the request of the Medical Adviser to the Controller for Development and Welfare, I visited Jamaica, Trinidad, British Guiana, Grenada, St. Lucia and Barbados in April and May, 1948. The object of the visits was to investigate leprosy in these colonies and advise regarding its treatment and control. Short reports were prepared after investigations in each colony and submitted to the local governments and the Controller. These are here abstracted and condensed. Reference may be made to reports of previous visits.*

Leprosy in the British West Indies (including British Guiana) must be studied from the background of the whole Caribbean Area, in some other parts of which the disease is much more prevalent than in the British Colonies themselves.

Leprosy is not a problem of major importance in the Britsh West Indies. There is however a growing feeling that just on that account it should be eliminated, if that can be accomplished without unduly depleting resources required for other more serious and urgent health problems. The highest prevalence is in Trinidad and British Guiana, in each of which there are calculated to be 1000 or more cases (0.3 to 0.4 per mille), but in Jamaica and in the smaller islands (Leeward, Windward, Barbados) it is considerably less.

Leprosy is associated with a shifting population. In the settled village everyone knows everyone else, and anyone suffering from leprosy is likely to be avoided by his neighbours, though he may infect his own family. But in a shifting population, especially the labour personnel of large industrial concerns (oil fields, sugar factories, etc.), everyone rubs shoulders with all and sundry, and the spreader of infection is less likely to be recognised and avoided.

Also those who go abroad, either for work or to visit relatives, not infrequently unconsciously contact infectious cases and acquire the disease. This was particularly seen in St. Lucia, where the majority of cases had been in direct or indirect contact with French Guiana, a country where leprosy is particularly prevalent.

SULPHONE TREATMENT.

There is reason to hope that the whole question of the control

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* *Leprosy Review* (1942), **13**, 22; (1943) **14**, 4, 18, 25, 29, 33, 39; (1944) **15**, 35, 40, 43.

of leprosy will be considerably modified by the introduction of sulphone therapy.

I spent four years (1941-1945) as Medical Superintendent of the Trinidad leprosarium, but it was only during the last seven or eight months of that period that the patients were on sulphone treatment. I found on my return after three years absence that many patients who, under the pre-sulphone regime would have been dead, blind, bedridden or permanently disabled, were now stronger and healthier, engaged in active work, and making obvious progress towards recovery. Lepromatous ulcers, once so common, had now almost entirely disappeared, and even trophic lesions had greatly diminished.

In the Jamaica leprosy institution the change for the better was also very noteworthy. Lepromatous ulcers caused by the breaking down of nodules and thickened skin lesions, formerly a marked feature, were absent, though the scars could still be seen. Also the distressing conditions of the nose and throat were absent, as were to a large extent those of the eyes. This was undoubtedly due to the introduction of sulphone treatment only nine or ten months before. The results were the more surprising as a shortage of supplies had interrupted the treatment for one or more months at the end of 1947. Of over 90 active cases of the malignant (lepromatous) type on promin or diasone treatment, 35 showed marked improvement in healing of ulcers, flattening of nodules, and clearing up of the nose and throat. In 30 others there was a distinct, though less marked, improvement. All these patients felt considerable improvement in general health. In several cases progressive deterioration of the eyes had become arrested.

An important fact is that the treatment in Jamaica was carried out by the Sisters in charge with practically no supervision from a physician. This is not mentioned as an ideal arrangement, but it emphasises the importance of intimate knowledge of the symptoms and natural course of the disease. Without this it is difficult to regulate the treatment. The Sisters have acquired this knowledge through years of careful observation of the patients. As a result, in combination with simple clinical laboratory tests, it has been possible for them to carry out the treatment without mishaps and with considerable efficiency.

In British Guiana the results appeared similar to those in Trinidad and Jamaica, the main difference being that there was in the leprosarium a far larger proportion of non-lepromatous cases (40 per cent) unsuitable for sulphone treatment. Partly for this reason the morale of the patients was less high at the time of my visit.

In Barbados, which I visited last, and where I made only a very short stay, sulphone treatment (diasone) had been introduced 5 months previously. Encouraging results had been obtained in the few patients treated for that period. In Grenada and St. Lucia sulphone treatment had not begun.

FACTORS IN THE SPREAD OF LEPROSY.

The countries and colonies comprising the Caribbean area show a varying incidence and may conveniently be divided under three categories: those in which leprosy is a major problem, such as Colombia and French Guiana; those in which there is a moderate incidence, such as Cuba, Trinidad, British and Dutch Guiana; and those in which the spread of the disease is slight, most cases arising through direct or indirect contact with the more affected areas.

So far, control in the small islands of the third category has aimed at isolating known cases in asylums which cost the government a large amount *per capita*, and yet are too small to justify expert medical, nursing and general care. These places have in consequence been avoided by patients, who have remained in concealment, often spreading the disease to their families and neighbours for years before being found and interned.

NEW PHASE IN LEPROSY CONTROL.

There is now a prospect that the more effective treatment of leprosy with sulphones may justify a radical change of policy, at least in places where leprosy is of low endemicity.

(1) The policy would aim at the abolition of leprosy asylums as soon as possible and, instead, would encourage patients to come forward early for treatment before they have become a danger to their associates. In other words, the increased attractiveness of treatment would take the place of compulsion. Uninformed members of the public might raise objections to open cases being allowed to live at home, not realising that at present there is often a gap of two or three years between becoming infectious and being isolated. The new system would aim at closing, or at least diminishing, this gap by attracting the patient to treatment at the earliest stage.

(2) To carry out this policy effectively it would be necessary to send two of the medical staff in each colony to undergo a thorough period of study in a suitable centre for at least three months, so as to become familiar with the diagnosis, classification and treatment of leprosy. These doctors would then be available

for consultation, and would be responsible for seeing that both prophylaxis and treatment were effectively carried out.

(3) All persons arriving from endemic countries would be kept under supervision, as would also contacts with known indigenous open cases. Periodic examinations would be made and patients, relatives and others taught the danger of infection.

This method, when once under way, would, it is hoped, be both more effective and less expensive than the present method. Open cases, who were found willing and able to co-operate in isolating themselves at home, would be given domiciliary treatment, if necessary free of charge. Otherwise they would be lodged in an annexe to an infectious diseases or general hospital.

The above scheme is proposed only for countries where the incidence is slight and the majority of cases are immigrants, or have acquired the disease abroad. Where the incidence is higher, as in Jamaica, British Guiana and Trinidad, it would be a mistake at the present stage to abolish institutions for isolation.

At the same time these institutions should be made more attractive. Those without experience are apt to think that attractiveness depends entirely upon food, accommodation and amusements. But still more important is the employment of the patients in useful work carefully adapted to their capacity, talent and interest. In Jamaica and British Guiana I found in the leprosy institutions large proportions of patients in whom the disease was no longer active, and who had no need for isolation. A few of these could not be discharged because of disabilities. The majority however were able-bodied, and were to a large extent taking advantage of their former disease to exploit the resources and comfort of the institutions. At the same time they formed a discontented and unruly element which constantly interfered with the good conduct of the patients. In both places the policy of retaining these patients was imposed contrary to the advice of those in charge. In Trinidad, on the other hand, this element had been discharged, making room for those requiring isolation, and the general morale of the institution was better on that account.

CORRESPONDENCE

THE EVOLUTION OF LEPROSY AND LEPROSY CONTROL.

The Editor, 19th June, 1948.
Leprosy Review.

Sir,

After doing other work for a few years, I am working again as a leprosy research worker, now in West Africa instead of India.

Fifteen years ago and more, the idea was taught and widely accepted (among British workers at any rate) that the form of leprosy now known as lepromatous was frequently a development from the form now known as tuberculoid. In my early days as a leprosy research worker, I, with others, regarded this as a reasonable view. Later, however, I began to have my doubts, and I began to study cases very closely over a period of years to obtain evidence bearing on this matter.

As this study went on, it became clear that a change from the tuberculoid to the lepromatous form of the disease was rare, and when I left the work in 1943 I could not say that the change had been clearly demonstrated in a single case; moreover, a study of the onset of the disease indicated that, while the very early signs of leprosy might be of rather an indeterminate nature, the lepromatous cases usually became definitely lepromatous at an early stage in their evolution and without any preliminary tuberculoid stage. These experiences in Calcutta were confirmed by our studies of leprosy in the Rural Leprosy Investigation Centre at Bankura, Bengal, where several hundred cases of leprosy were studied clinically, bacteriologically and immunologically, most of them untreated, from 1937 onwards. An important point coming out of this study was the finding that the tuberculoid cases remained tuberculoid, that the lepromatous cases either started as such or became lepromatous after a relatively short phase which was definitely not tuberculoid.

Conversely, with the subsidence of lepromatous lesions, patients, in my experience, do not develop tuberculoid lesions.

I should, however, mention a group of cases in Calcutta which was included in the study and which did not appear at one time to support the idea of a change from tuberculoid to leproma. These cases showed localised thick lesions closely resembling major tuberculoid lesions clinically, but on closer study there were seen certain differences which may be summarised as follows: the lesions tended to be more numerous and scattered throughout the body

than the tuberculoid lesions which frequently, in Calcutta, numbered only one or two; the edge of the lesion was not as clear cut as in the typical tuberculoid lesions; the surface of the lesion was smoother, and the feel of the lesion was softer and more succulent; the involvement of nerves supplying the lesion was less marked, and the loss of cutaneous sensibility was less complete; the lesion always showed a moderate, and sometimes a large number of bacilli, instead of the occasional finding of a few bacilli only at certain times which is characteristic of a tuberculoid lesion in India. The lepromin test in these cases gave a negative, doubtful, or occasionally a weak positive result, contrasting with the strong positive result in the major tuberculoid cases which they resemble. On histological study, these lesions showed a most strange picture, some microscopic fields appearing typical tuberculoid, with giant cell systems and so on, while other, often adjacent, microscopic fields showed typical foamy cell leproma. I remember on at least one occasion seeing what looked like typical tuberculoid and typical lepromatous histology in the same oil immersion field.

I called these cases " mixed " cases, not in the old sense of the word as applied to cases of leprosy to indicate that both nerve and skin lesions were present, but in a new sense to indicate that in the lesions were found some features indicating a lepromatous nature, as we now understand these terms. It became clear that the prognosis of these cases was relatively poor. Moreover, I never saw these " mixed " features develop in a patient who had previously shown only typical tuberculoid lesions.

On the basis of this experience, I came to my present view, which I hold until definite evidence is produced to the contrary:—

1. Tuberculoid cases start as tuberculoid cases or become tuberculoid quite early, and they remain tuberculoid throughout.

2. Lepromatous cases also start as such or become so early, with no previous tuberculoid phase, and they remain lepromatous throughout.

3. There are other cases which are neither typical leproma nor typical tuberculoid, but from an early phase show some of the features of both as outlined above. These features do not indicate that a change from tuberculoid to leproma is in progress; these cases appear to be in a class by themselves, more allied to leproma than to tuberculoid, and possibly sometimes developing into typical leproma.

In the differentiation of atypical and anomalous cases I believe

that the lepromin test, particularly in its improved form, with the bacillary antigen standardised by weight by the methods of Dharmendra, to be of very great use.

The treatment with sulphones, with all its grave limitations, at any rate does mean that the treatment of the lepromatous case is not the heartbreaking task for the physician and for the patient that it sometimes used to be. We should not now see so many patients getting steadily worse in spite of all that we can do. We still have a long way to go, but surely it is not foolish optimism to hope for further developments. My experience of leprosy treatment with sulphones is limited as yet, but I have already seen results such as I have not seen in over twenty years experience with other treatments.

I am, Sir,

Yours faithfully,

JOHN LOWE.

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DR. R. G. COCHRANE, CHINGLEPUT, S. INDIA, COMMENTS AS FOLLOWS :—

The report of the Commission on Classification at the Cuba Leprosy Congress was divided into three sections, (1) Introduction, (2) Classification and definitions and (3) Clinical sub-divisions. The report of this commission will be a great disappointment to those who were looking for clarity and an authoritative statement on the subject. Because of the divergence of views, not in matters of academic detail, but in matters of terminology the last section of the report, viz., Clinical sub-division, was rejected by the plenary session. The chief objections to the detailed classification placed before the Congress were (i) The term "tuberculoid" was used to denote a histologic picture, but in every clinician's mind tuberculoid leprosy is a clinical entity which can be recognised without resources to histology if facilities are not available. Admittedly clinically tuberculoid lesions have a tuberculoid histology, but to base the diagnosis of a tuberculoid lesion mainly on histology, will I believe, lead to gross errors. There was, however, universal agreement on several points and it is hoped that as a result of many private discussions, leprologists the world over will give serious thought to this question which will result in a more practical and generally accepted classification. It was generally

agreed that there were essentially two polar forms in leprosy one tuberculoid, resistant and unlikely to change; and the other leproma, non-resistant and difficult to treat. There was considerable discussion, mostly privately, as to whether "tuberculoid" meant the same to all, some including the writer, believe that the "tuberculoid" picture which was described is not a composite one and this accounts for the claims by some workers that tuberculoid can turn into leproma, or the more extraordinary view that leproma under certain circumstances can become tuberculoid. Not until there is more general agreement as to the histological interpretation of tuberculoid will there be any real chance of agreement as to the evolution of these lesions. For the time being workers are advised to adhere to the Cairo classification and await as patiently as possible further elucidation on this vexed problem. In the subdivision of classification no place was made for the border line lesion (Wade), intermediate (Cochrane) or doubtful lesions (Lowe & Dharmendra). These workers have written extensively on the subject and there is being built up a general conception of these lesions which merit special mention in an intermediate classification. In the writer's opinion there are two quite separate clinical entities in the tuberculoid classification, that is if the word is to be used with a histological and immunologic connotation. These can be divided into:

(a) Tuberculoid lesions which are clear cut, which are always raised with a well marked periphery, and frequently a healing centre; the lesions may be in a form of a plaque, or in the minor variety "pebbled," to use Wade's term. These are always lepromin positive with a granuloma focal in its distribution with epithelioid cells and giant cells and with no free sub-epidermal zone.

(b) Tuberculoid lesions which are more succulent in appearance, again to use Wade's term, with edges much less distinct, oedematous, and looking more like leproma than tuberculoid; lesions in the ears are particularly like leproma. The histologic picture is basically tuberculoid with the granuloma distributed as in leproma, and with a marked tendency to, or frequently actual formation of a clear sub-epidermal zone. These lesions are not always in reaction, though when in reaction mixed histology—leproma and tuberculoid—is frequently seen, These two pictures are very different from the clinical, histologic, and prognostic point of view. The former is truly polar, lepromin positive, remaining true to type and not changing to leproma, or so rarely—I have never seen a case—that one can make this statement. In the latter the lepromin is variable, frequently negative,

and with a definite tendency to change over to leproma, and I believe may also revert back to the tuberculoid type of histology; on this I would not be dogmatic. To place both these lesions in the tuberculoid classification is confusing, so why abandon the logical term " Border Line, intermediate or doubtful "?

CONTRIBUTION FROM DR. GEORGE L. FITE, CARVILLE, U.S.A. :—

One of the questions raised by Dr. Lowe is the interesting one of the co-existence of lepromatous and tuberculoid changes in the same lesion. We have seen a fair number of examples of this. The cases are, for the most part, lepromatous in character, and in the tissues the lepromatous changes are rather more prominent than the tuberculoid. If left alone, it is my impression that these cases continue as lepromatous cases, and that further development of tuberculoid changes is unlikely, especially in adults. The question is immediately raised: were the cases ever tubrculoid? Did the lepromatous change follow a tuberculoid phase? Dr. Lowe says no, and all I can say is that I have not seen the change take place. Although the evidence is unfortunately indirect, there is basis for believing that both tuberculoid and lepromatous appearances in the tissue began together, and one must assume that this is the case, until or unless examples can be followed from one to the other. Dr. Lowe suggests calling such lesions " mixed." I have no better suggestion to make, although the expression is not a good one, simply because the term has been used and is being used elsewhere in leprosy to mean another thing altogether, and students of leprosy are not always clear, when they get into the subject of nomenclature, whether they are discussing the case or the lesion.

With further regard to these lesions, the question may be raised as to the " normal " extent to which tuberculoid changes occur in lepromatous lesions. The furore for tuberculoid leprosy has, I fear, caused us to neglect the lepromas as being banal lesions of no especial interest. Yet, we have the feeling that, when the leproma is properly examined in its early stage, perhaps this sort of thing is not so unusual after all. Perhaps in the early outbreak of the disease, before an immonologic status is well defined, before the disease is far advanced, some admixture of " types " of cellular reaction is to be expected. As one's experience with leprosy accumulates, one gradually acquires the impression that leprosy as it grows older becomes fixed as to type. We do not expect the well established case to change, be it tuberculoid, lepromatous, or even one of those cases which cannot on the

basis of present day understanding be properly categoried. There seems to be, however, a phase in the leprous process during which some change, not great, may take place in the type of lesion. Our knowledge of the evolutionary early phases of leprosy, especially from the histologic view, is still far from being properly documented under the microscope, and judgments as to typing different examples of tuberculoid leprosy from the scientific standpoint are necessarily immature.

COMMENTS BY DR. E. P. FIDANZA, ROSARIO, ARGENTINA :—

Lowe's paper deals with particularly important subjects such as the onset of leprosy, the change from one form to another, intermediate cases, the value of the lepromin test, and present measures of prophylaxis. His paper is specially welcome as it summarises his opinions based on his recognised experience, which he was not able to present at the last international congresses.

My opinion on each matter is as follows:—

(1) As regards the forms of onset, I believe leprosy always begins with a simple inflammatory lesion of an undifferentiated or indeterminate type[1] which manifests itself clinically as flat macules, either hypochromic, erythemato-hypochromic or erythematous, and histologically as of simple inflammatory structure, that is to say, with privascular, perineural, etc. round cell infiltration. The later development of the disease depends on the degree of resistance with which the body can oppose the M.L. When there is sufficient resistance, the disease will be arrested in this first stage, or regress without further clinical manifestations (abortive infection), or perhaps develop as the tuberculoid form. When there is no resistance the disease will progress towards the malignant type of leprosy. Finally, when the body is indifferent, that is to say, neither resistant nor favourable to the invading germ, the initial lesion will remain stationary, providing a simple indifferentiated case.

(2) The result of the " lepromin test " is intimately related to the way in which the organism reacts to the infection, and thus provides a valuable aid in the classification of the type of leprosy.

I agree with Lowe that well defined reactions (that is to say definitely positive or negative) are only slightly modified during the course of the disease. Nevertheless, though I have not seen a definitely positive reaction change to negative, I have seen lepromatous cases, and even more frequently indeterminate ones,

originally lepromin negative, become lepromin positive when submitted to vigorous and prolonged treatment, their lesions disappearing.

(3) As regards the change from one type of leprosy to another, I admit I have thought of Lowe because of his reply to the enquiry made by Schujman[2] in 1936 in the International Journal of Leprosy, and from other articles [3] [4] [5] [6], as holding the belief that tuberculoid leprosy can change to the lepromatous form. He now clarifies his opinion on this matter.

I have never seen a typical tuberculoid case with follicular structure, circumscribed cutaneous lesions, and definitely positive lepromin reaction change into the lepromatous form. If such a change should occur, in my opinion, it is exceptional. This was my answer to the enquiry in the Journal and I still think the same.

The typical lepromatous type also tends to remain as such or regresses under treatment without changing to tuberculoid. Nevertheless I have seen, though very exceptionally, a clinical and histological lepromatous form. Souza Lima[7] has also observed lepromatous forms change to tuberculoid in patients treated with sulphones.

To sum up, I believe that, though no type of leprosy is absolutely immutable, a direct and spontaneous change from one polar type to another is a rare exception.

Souza Lima and Castro Cerqueira [8] have shown that when this change does occur the rule is that the lepromatous form does not change directly to the tuberculoid, but passes through an undifferentiated stage, i.e. lepromatous-undifferentiated-tuberculoid, or vîce vêrsa.

It is possible that treatment with new drugs will increase the frequency of the change from lepromatous to tuberculoid. Souza Lima has already collected observations which show favourable changes, and we have also proved them histologically in two cases at least. [1]

(4) I agree with Lowe that there are cases clinically and histologically resembling in some aspects the lepromatous types, and in others the tuberculoid, almost always lepromin negative, having a fair number of bacilli round the lesions, which have been called " borderline " by Wade and Rodriguez [9], " intermediate " by Cochrane [10] and " N C " by Lowe himself [11].

An outstanding characteristic of these intermediate cases is that they are almost continuously in a reactive state, thus appearing very similar to the cases with tuberculoid leprous reaction described

by Wade [12], Schujman [13] and Fernandez [14]. Souza Campos has described a form of leprous reaction which he calls " reactional tuberculoid " with a similar picture to that of these " intermediate " cases in their reactive stage.

I do not believe these cases constitute another type *per se*, but regard them as reactive states or stages in the disease. They form a third type of reaction, " intermediate or borderline leprous reaction ", intermediate between the " tuberculoid leprous reaction " of Wade, Schujman and Fernandez, which is seen in typical tuberculoid forms, and the classical " Lepra reaction " or " lepra fever " of the lepromatous forms. They are closer to the former in their clinical appearance, histological structure and subacute development, and to the latter in the general symptoms, the number of bacilli in the lesions, and the poor prognosis.

(5) I agree with Lowe that measures of control should be chiefly concentrated on the lepromatous or potentially lepromatous forms.

Finally, I agree with Lowe's opinion regarding progress in therapeutic measures. I believe the advent of sulphones have brought a new era, and even if it does not mean a solution of the problem, it certainly opens new paths full of promise.

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2. Schujman, S.—" Classification and evolution of tuberculoid leprosy ".—*Internat. Jour. Lep.* **4**, 369-and 375, 1936 (correspondence).
3. Lowe, J.—" In a symposium on: Classification and evolution of tuberculoid leprosy ".—*Internat. Jour. Lep.* **4**, 371-372, 1936 (correspondence).
4. Lowe, J.—" A note on tuberculoid changes in leprosy as seen in India ".—*Internat. Jour. Lep.* **4**, 195, 1936.
5. Lowe, J.—" A study of macules in nerve leprosy with particular reference to the tuberculoid macule ".—*Lep. in India* **8**, 97, 1936.
6. Lowe, J.—" A note on racial variations in leprosy with particular reference to Indian and Burmese races ".—*Lep. in India* **10**, 132, 1938.
7. Souza Lima L. y Castro Cerqueira, G.—" Tratamento experimental da lepra pelas diamino-di-fenil-sulfonas " II° *Conf. Pan. de Lepra—Rio de Janeiro* 1946—Vol. II pag. 9.
8. Souza Lima L.—" Sobre a classificaçao Sul-Americana das formas da lepra ".—*Rev. Bras. Lepr.* **13**, 135, 1945.
9. Wade, H. W. and Rodriguez, J. N.—" Borderline tuberculoid leprosy "—*Internat. Jour. Lep.* **8**, 307, 1940.
10. Cochrane, R. G.—" Development of the lesions of leprosy. With particular reference to tuberculoid leprosy and the significance of the lepromin test ".—*Internat. Jour. Lep.* **8**, 445, 1940.
11. Wade, H. W. and Lowe, J.—" The type distribution of patients at the Purulia Leper Colony ".—*Lep. in India* **9**, 39, 1937 (Foot note by J.L.)
12. Wade, H. W.—" Lepra reaction in tuberculoid leprosy ".—*Internat. Jour.* Lep. **2**, 219, 1934.
13. Schujman, S.—" Reacción leprosa tuberculoide ".—*Rev. Arg. Dermat.* **19**, 411, 1935.
14. Fernandez, J. M. M.—" La reacción leprosa tuberculoide ".—*Rev. Bras.* Lep. **5**, 419, 1937.

DR. DHARMENDRA, CALCUTTA, INDIA, COMMENTS AS FOLLOWS :—

In his letter Dr. Lowe has raised certain important points regarding the evolution of leprosy and has referred to the work that has been carried on at the Leprosy Department of the Calcutta School of Tropical Medicine, with which he was associated up to 1943. In general I am quite in agreement with the views expressed by Dr. Lowe, except for some minor differences in the matter of details. It would be useful to very briefly quote the findings made in our studies, before offering any comments on the above letter. These studies have been carried on at a field investigation centre at Bankura in West Bengal, and at the School in Calcutta.

STUDIES AT THE LEPROSY INVESTIGATION CENTRE, BANKURA.

At this centre epidemiological studies in leprosy have been in progress since 1936. The centre is situated in a highly endemic district of Bengal, and comprises 40 villages with a population of about 10,000, with an incidence of leprosy of 4.5 to 5%. The number of cases at any one time in the area has varied from 425 to 500, of which only about 20% are of the "lepromatous" type, and the remaining 80% of the "neural" type including flat patches, thick patches (tuberculoid) and a small number of cases with only sensory changes and no patches. One of the functions of the centre has been to follow up the known cases by repeated clinical, bacteriological and immunological (lepromin test) examinations; no histological examinations were however made. During the period of study a change of type has been seen in about 2.5% of the total number of the neural cases (11 cases), and in none of these cases was there any evidence of the lesions having been "tuberculoid" as judged by clinical and immunological findings. Clinically one case had only sensory changes in an extremity without any patches, and the remaining 10 cases had ill-defined macular lesions; the lepromin reaction in all these cases was negative, both before and after the change.

STUDIES AT THE CALCUTTA SCHOOL OF TROPICAL MEDICINE.

The findings made in a follow up study of two groups of cases have a bearing on the points under discussion. The first group consisted of cases with the lesions not being typical of either the tuberculoid or the lepromatous type, but having some features of both; and the other group consisted of cases with what looked like "tuberculoid-reacting" lesions. The follow-up study has covered several years, and has included repeated clinical, bacteriological, histological and immunological (lepromin test) examinations. The classification in more than half of the cases

in the two groups has been cleared up by means of the studies, a majority of the cases in the first group being lepromatous, and that in the second group tuberculoid. However, there have been cases in both the groups which still remain " Unclassified " even after prolonged study.

In these " unclassified " cases, the clinical, bacteriological, histological features all appear to be in an unstable state, and perhaps these cases form a group by themselves. Histologically, there were elements of both the tuberculoid and lepromatous histology, though usually neither of these were marked; clinically early subsidence was usual, but was often followed by a relapse; bacteriologically all the cases showed moderately large numbers of bacilli in the beginning, which diminished with the subsidence of the lesion, but continued to be found for long periods even after the clinical subsidence of the lesions; the results of the lepromin tests have been variable, and considerable variations have been seen in the same cases in different stages of activity. In these cases it was usual to find a considerable reaction to lepromin associated with greater activity of the lesion, and a weaker reaction associated with the subsidence of the lesion.

Thus in these "unclassified " cases the clinical, bacteriological, histological and immunological findings have been mid-way between the lepromatous and tuberculoid groups. A point of special interest amongst the group has been the change seen in two cases to the lepromatous type. In the beginning the lesions in these two cases were localised and smears from them showed only small numbers of leprosy bacilli; after a considerable period of time; large numbers of leprosy bacilli. The histological examination of biopsy material in the beginning was originally reported as tuberculoid, but on re-examination the findings were not considered clear cut and the sections were reported as " doubtful ": but later (when clinically lepromatous) biopsy material showed lepromatous histology. The lepromin test in both these cases was negative.

The above two cases illustrate a change to lepromatous of lesions which in the beginning looked " tuberculoid ", but were not really so as judged by immunological and histological findings, In the absence of a critical outlook the changes seen in these cases could have been interpreted to illustrate a change from tuberculoid to lepromatous, which actually it was not.

BEARING OF THE ABOVE FINDINGS ON THE QUESTION UNDER DISCUSSION.

The findings made in the studies quoted above bear on most

of the questions raised in Dr. Lowe's letter, and I will now attempt to deal briefly with them.

1. *Can a "tuberculoid" lesion change into lepromatous?* It would be apparent from the results of the above studies that the answer to this question is tied up with our conception of the word "tuberculoid". This term was originally used by Jadassohn to indicate the tuberculoid nature of granuloma which was seen in some leprous lesions. But to most leprosy workers it has come to mean much more than that; instead of the tuberculoid structure, the leprosy worker of to-day thinks in terms of the "tuberculoid case" indicating thereby not only the histological picture of the lesion, but also the clinical, bacteriological, immunological, and prognostic aspects of the disease in that case, although in most cases this classification of the case is made usually on the clinical grounds.

If the first interpretation is accepted and the term tuberculoid is used to indicate the presence of tuberculoid structure in the leprous granuloma, one can say that the change from tuberculoid to lepromatous does occur. But if, on the other hand, the term tuberculoid is used in the restricted sense of a "tuberculoid case", the change from it to lepromatous must be a rare thing, if it occurs at all.

With these considerations in view, I think that reports of a tuberculoid case becoming lepromatous should be accepted only after close scrutiny. The two cases (referred to earlier in this letter) are an illustration of this point; in the absence of a critical outlook these two cases could have been reported as tuberculoid cases becoming lepromatous which they were not, if the conception of the "tuberculoid case" is accepted. It would be too dogmatic to say that this kind of change never takes place, but this much is certain, that a true "tuberculoid case" very rarely becomes lepromatous, and that for practical purposes this possibility can be ignored. (I feel however that the term tuberculoid with its two different interpretations is a very unsuitable one, and hope to make it the subject matter of a future communication.)

2. *Change from lepromatous to tuberculoid.* This question is again bound up with the interpretation of the term tuberculoid. It is true that tuberculoid structure is occasionally seen in biopsy material from a lepromatous case, but that does not mean that the case was or has become "tuberculoid".

3. *Variations in the results of the lepromin test.* In early publications on the lepromin test from the Leprosy Department of the School of Tropical Medicine, Calcutta, it was reported that only

minor variations are seen in the results of repeated tests on individual cases. However, the long term study of cases has shown that occasionally, though not commonly, the variation in the reaction may be of a major degree; a once negative reaction may sometimes change to a positive one, or vice versa. The change from negative to positive lepromin reaction has been seen in cases with neuromacular "simple" lesions with further progress of the disease, and in a small proportion of lepromatous cases a considerable time after their subsidence. A change from positive to negative lepromin reaction has sometimes been seen, especially in the "unclassified" cases referred to earlier in this note. Some of these cases had a positive lepromin test when seen first in an active state; with the subsidence of clinical activity the reaction to lepromin becomes weaker and may ultimately become negative; it may again become positive with a relapse of increased clinical activity.

4. *Evolution of the disease.* My experience in India is in complete agreement with that of Dr. Lowe regarding the evolution of the disease, and I quite agree with him that in our attempts to control the disease our efforts should be concentrated on the open (infective) case.

THE PREPARATION OF CARBOL-FUCHSIN FOR ZIEHL-NEELSEN'S STAIN.

W. R. BALE

At the request of Dr. E. Muir a method of preparation of carbol-fuchsin for Ziehl-Neelsen's stain which has been particularly successful for the demonstration of leprosy bacilli is described. Basic fuchsin is obtained from a source which can supply a stain of a reasonably standard composition.

Basic fuchsin	10 gm.
Absolute ethyl alcohol	100 ml.
Phenol	50 gm.
Distilled water	950 ml.

Boil the basic fuchsin with absolute alcohol under a reflux condenser for thirty minutes. Allow to cool. Mix phenol with water until dissolved. Add to the alcoholic solution of fuchsin and shake well. When the fuchsin-alcoholic and phenol solutions are mixed a precipitate starts to appear at once and continues for a period of 3—5 days. The stain should not be used during this time. After 5 days the stain is filtered and is ready for use. It keeps well for at least nine months, the longest period for which there has been occasion to store it in this laboratory.

REVIEWS

The Lancet, No. V of Vol. II, 31st July, 1948.

Treatment of Tuberculosis with Sulphetrone—D. J. Madigan. p. 174. A detailed and careful study. (Readers should note that dosages and blood levels of sulphetrone recommended in tuberculosis may be dangerously high in the treatment of leprosy.—Ed.) The author summarises as follows.—

"In 70 cases of tuberculosis affecting different organs sulphetrone was given for periods which varied from a few days in tuberculous meningitis to eighteen months in more chronic cases.

Whether sulphetrone is given parenterally or by mouth, a gradual increase of dosage is necessary to build up therapeutic blood-sulphetrone levels of 7·5—10 mg. per 100 ml. if toxic symptoms are to be avoided.

It is also essential to give iron and brewers' yeast to avoid hypochromic and nutritional anaemia. Even so a residual haemolytic anaemia will arise, leading to a fall in haemoglobin concentration though not to below 60% (Haldane).

To avoid major toxic emergencies, seen when blood-sulphetrone levels above 12·5 mg. per 100 ml. are allowed to persist, a scheme of management is suggested.

In general no beneficial effect was detected from sulphetrone therapy of acute infections—e.g., acute miliary tuberculosis and tuberculous meningitis—but a patient with chronic miliary tuberculosis recovered. On the other hand, improvement was observed in chronic lesions. Thus 12 out of 17 cases of acute pulmonary fibrocaseous disease, and 13 out of 22 chronic cases, improved. All of 4 cases of primary pulmonary tuberculosis, and 6 out of 8 strictly exudative lesions, improved. In the chronic haematogenous group all of 4 cases improved, and in the productive pulmonary infiltrative group 3 out of 4 improved.

In general, all exudative phases of infiltrative disease were halted and reversed by sulphetrone.

The need for long-continued courses is emphasised, units of observation being three months, and routine laboratory control is essential.

Sulphetrone is useful as an adjuvant with definite objectives in view."

Chemotherapy of tuberculosis with Sulphetrone.—Clay & Clay. p. 180. A report on the treatment of 44 tuberculosis patients with sulphetrone over a period of two-and-a-half years. (Again it should be noted that the dosages of 6-12 g. daily used in this experiment do not indicate that similar doses should be used in leprosy.—Ed.) The authors summarise as follows:—

"Sulphetrone was given to 57 patients with tuberculosis. Only 44 of these cases, 42 of which were pulmonary, were treated long enough for the results to be assessed.

Improvement was noted in 22, 5 were unchanged, 6 became worse, and 11 died. Of those who improved, 9 improved considerably, 7 moderately, and 6 slightly. Improvement was not dramatic, and at best sulphetrone can only be regarded as an adjuvant and not in any way a specific for tuberculosis.

Sulphetrone produced toxic side-effects (nausea, vomiting, anorexia, headache, depression, drug rash, and disturbances of vision) in 6 out of 57 patients. These effects disappeared on the withdrawal of the drug.

Sulphetrone lowers the haemoglobin level, but this can be corrected by iron and yeast.

Sulphetrone should be used only if there are facilities for estimating blood-sulphetrone levels and for carrying out blood-counts.

Further trials with sulphetrone in selected cases are warranted."

LEPROSY REVIEW. VOLUME XIX.

INDEX TO VOLUME XIX. (1948).