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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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.
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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.