LEPROSY REVIEW

The Quarterly Publication of
THE BRITISH LEPROSY RELIEF ASSOCIATION

VOL. XXV. No. 3 JULY, 1954.

Principal Contents

The Late Results of Sulphone Treatment of Leprosy in East Nigeria

The Sixth International Congress of Leprology, Madrid

Reports and Notes

Reviews

8 PORTMAN STREET, LONDON, W.1

Price: Three Shillings and Sixpence, plus postage
Annual Subscription: Fifteen Shillings, including postage

LEPROSY REVIEW.

VOL. XXV, No. 3. JULY, 1954.

CONTENTS

PAGE

Editorial 111

In Memoriam. Dr. G. Gushue Taylor 112

The Late Results of Sulphone Treatment of Leprosy in East Nigeria. JOHN LOWE 113

The Sixth International Congress of Leprology, Madrid 125

Technical Reports: Classification 127

Treatment 132

Immunology 136

Epidemiology and Control 140

Social Aspects 144

Notes on some Papers presented at the Madrid Congress 146

Reviews 159

Correspondence 167

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EDITORIAL

PERSONAL

As is recorded in our last issue, a new Editor is now responsible for this Review. The Editor wants to make this Review as good as he can, which means that it must be of real practical value to those actively engaged in leprosy work. At the same time less practical aspects of the subject should not be ignored. A new editor likes to take over and find a stock of suitable manuscripts of original material awaiting his attention. That is not the new editor's lot, for the cupboard is bare.

THE MADRID CONGRESS

Fortunately for the present issue the reports on the Madrid Congress are now coming in. These provide most of the material in the present issue, for our pages contain a personal report on the conference, a review of the Madrid Congress number of the *International Journal of Leprosy* and also some notes on interesting points in the papers presented at the Congress. Thus it is aimed in the present number to cover the Madrid Congress fairly fully in broad outline. Many readers will however want more detail than we can give here, but for this they must consult the *International Journal of Leprosy* or the Congress Proceedings when they are published.

THE LATE RESULTS OF SULPHONE TREATMENT

On the whole it is surprising that although sulphone treatment has now been used in certain centres for up to thirteen years, very few reports have appeared on the later results of treatment, and on the question of relapse and its frequence and severity. There are various reasons for this. In some centres the treatment has not been used long enough; in some centres the number of cases has not been sufficient; sometimes it is not possible to get patients to come for re-examination after discharge; sometimes records of cases treated years ago are inadequate; sometimes changes of staff or shortage of staff have made the long continued observation and records difficult to maintain. Nevertheless, it is felt that there

must be those who have the records of a sufficient number of cases treated for a long enough period, and examined after discharge for relapse. Analysis of these records should give information of value. Our present issue contains a report based on such an analysis of such records; the findings are most encouraging.

The report itself tries to make clear that the work recorded has been done under very favourable conditions, which are hardly likely to be duplicated elsewhere. Moreover, the work has been done under the very close personal supervision of the writer for nearly the whole of the time of the study—eight years.

There are a few other reports available on the late results of sulphone treatment. While it is generally agreed that the results are a great improvement on those obtained with previous forms of treatment, these other reports are less favourable than the present one. Two of these reports are discussed in the present report. We are trying to gather more information on this subject for presentation and discussion in future issues.

IN MEMORIAM

We have learned with deep regret of the death, on April 23rd, of Dr. G. Gushue Taylor, the founder of the Happy Mount Leprosy Colony in Formosa. Dr. Taylor was born in Canada, received his medical training at the London Hospital, and served as a missionary, first with the English and later with the Canadian Presbyterians. After his retirement he maintained his keen interest in the Leprosy Colony, and was returning from a visit to Formosa when he was attacked by acute appendicitis at sea, and died.

THE LATE RESULTS OF SULPHONE TREATMENT OF LEPROSY IN EAST NIGERIA

JOHN LOWE, C.B.E., M.D., F.R.C.P.

Late Specialist, Nigeria Leprosy Service
Medical Secretary, British Empire Leprosy Relief Association.

It is now thirteen years since sulphone treatment of leprosy was first used in the United States.[1] Sulphone treatment in various forms has now become the standard treatment of leprosy throughout the world. Many reports have been published covering the early results; a few reports[2, 3 & 4] cover a few years treatment, but the only report on late results of treatment available to me is that of Erickson,[5] which is discussed later.

The object of the present report is to present the late results of sulphone treatment of leprosy as seen in Uzuakoli, East Nigeria, in a large series of cases studied intensively for periods up to eight years.

THE CONDITIONS IN WHICH THE STUDIES HAVE BEEN MADE.

In assessing the value of any study of this nature, it is important to know the conditions in which the work has been done. The Ibo people of Eastern Nigeria are intelligent and progressive; they have known and feared leprosy for many generations and they can usually recognise the disease in its early stages; their village and clan organisations have greatly aided detection and treatment. Moreover leprosy has carried a great social stigmata, and patients are prepared to go to much trouble and often expense to get cured of the disease, and to get rid of the stigma. The people have great faith in modern medicine and in those who administer it; they insist on having treatment, and are reluctant to stop treatment even if complications arise. With modern chemotherapy of leprosy at any rate, the patients usually persist in the treatment until they can receive a medical certificate that the disease is arrested, although in some cases this has taken several years. Of well over 1,000 patients treated and accurately recorded by me during the last six years, not more than one dozen have left without permission; although about one hundred have for various reasons been transferred to treatment centres elsewhere.

Further, and most important, when treatment ceases on the patient's discharge, they are instructed to come for examination every 3 months for a year and, after that, every 6 months for a year or more, and most of them do this for a time at any rate.

If any relapse occurs, it is almost sure to be detected either at periodical re-examination, or at home by the patient himself or his relatives, in which case the patient comes demanding more treatment.

For these reasons I think that it is very doubtful if there is any other centre in the world where conditions are so favourable to the successful treatment of leprosy, or for the assessment of late results of treatment, and of relapse rates.

THE FORMS OF SULPHONE TREATMENT USED.

Sulphone treatment of leprosy was started here by Dr. T. F. Davey in March 1946, exactly eight years ago, in a small group of 43 patients, "diasone" being the drug used. Later that year another small group was treated with "sulphetrone." Later still diamino-diphenyl-sulphone (D.D.S., dapsone) treatment became established, first in the Research Unit, and later as the routine treatment in the settlement and its many clinics, as well as in other settlements and clinics in Nigeria. No attempt is made here to assess the results of this widespread treatment. Our present discussion deals only with those patients studied thoroughly and treated in our small Research Unit which was established in December 1947, took over the patients and records of Dr. Davey's previous work, and continued and developed it.

THE PATIENTS TREATED.

The patients treated by the Research Unit, which form the basis of this study, have been selected from the Settlement and from its many clinics because of the severity and activity of their leprosy or because of complications arising during treatment. They do not represent the ordinary leprosy of the area; they are selected as the most marked cases of leprosy we have been able to find, or as those most difficult to treat, with the exception that we have usually not selected patients so crippled and disabled that they could not attend our clinic for all the many examinations which our research work demanded.

The Late Results of Treatment.

In assessing the late results of treatment of leprosy, two questions are of paramount importance. These questions are (1) What is the present condition of those patients who were being treated several years ago, and in how many of them has the arrest of the disease been produced? (2) In those in whom the disease has been arrested, how many have later shown relapse? The present paper attempts to answer these two questions in relation to our patients here.

THE PRESENT CONDITION OF PATIENTS WHO STARTED TREATMENT BETWEEN MARCH 1946 AND MAY 1948.

These patients number 131, and we here account for the whole number, taking them exactly as they appear on our books with no omissions whatever. Of the 131 patients, 9 were bacteriologically-negative tuberculoid cases, and 122 were bacteriologically-positive lepromatous cases. The patients fall into three groups according to the time when they started treatment, and the form of treatment used.

(a). *Patients starting treatment in March 1946.*

These patients number 43. Of these, two died from gastro-enteritis before the disease was arrested, one patient absconded, and one was transferred for treatment elsewhere. 39 cases remained for analysis — 35 lepromatous cases and 4 tuberculoid cases.

Of the 35 lepromatous cases, 34 became and remained bacteriologically negative. Of these 34, 2 died, one from pneumonia and one from unknown causes, before discharge, 30 have been discharged, and 2 are bacteriologically negative and clinically inactive and awaiting discharge. Only one of the 35 is still bacteriologically positive, and that very slightly, although the disease is clinically inactive.

Of the 4 tuberculoid cases, all have long been discharged with the disease inactive.

To summarize: of these 39 cases, 2 died just before discharge, 34 have been discharged, two are awaiting discharge and only 1 remains positive.

(b). *Patients starting treatment during 1947.*

These cases number 36, 35 being lepromatous and 1 tuberculoid.

Of the 35 lepromatous cases, 31 are now clinically inactive and bacteriologically negative, 22 having already been discharged. Eight are awaiting discharge and 1 went away just before discharge. The remaining 4 lepromatous cases are clinically inactive, but still show a few bacilli in the lesions. Treatment is continuing.

The one tuberculoid case has long been discharged.

(c). *Patients starting treatment early in 1948.*

These number 52. Eight were transferred for treatment elsewhere, and 2 absconded, leaving 42 for analysis, 39 being lepromatous cases, and 3 tuberculoid. Of the 39 lepromatous cases, 32 are clinically arrested and bacteriologically negative, 25 of these having already been discharged and 7 are to be

discharged shortly. The remaining 7 cases, though clinically inactive, still show a few bacilli.

All the 3 tuberculoid cases have been discharged.

These three groups are below taken together and the findings recorded in tabulated form.

TOTAL CASES	131
Died before disease arrested	2
Absconded	3
Transferred for treatment elsewhere	9
Remaining for analysis	117
Lepromatous cases arrested and discharged	77
Lepromatous cases arrested awaiting discharge	17
Lepromatous cases arrested but died (2) or absconded (1) before discharge	3
Lepromatous cases showing clinical arrest but smears still show a few bacilli	12
Tuberculoid cases arrested and discharged	8
	117

Discussion.

From these observations one broad conclusion stands out. The response of leprosy to sulphone treatment is very slow, but amazingly sure. In not one of these 117 cases has the treatment failed to produce a definite and progressive improvement leading, in the course of years, to clinical inactivity and finally to bacteriological negativity. It is true that in many of these cases there have been periods, and sometimes quite long periods, when improvement has appeared to become negligible, and one has begun to wonder whether the lesions would ever become bacteriologically negative. The indications are that in time they all do.

Another most encouraging fact should be recorded. In none of these patients treated with sulphone have we observed the phenomenon of improvement occurring only up to a point, and then deterioration setting in; this phenomenon probably indicates the development of drug resistance, and is not infrequently seen in the chemotherapy of other infections—for example, in tuberculosis—and even in the chemotherapy of leprosy with agents other than sulphones. The fact that we have not seen this phenomenon does not prove that sulphone resistance of the leprosy bacillus is not seen at all, but it does indicate that, in East Nigeria at any rate, such drug resistance is mild in degree, and not sufficient to enable the infection to get out of the control of the continued administration of the drug in the usual doses.*

* See note at end of this paper.

I have, in fact, attempted to speed up the response to sulphones by giving doses larger than normal at different stages of treatment, including the later stage, and by combining sulphones with some other chemotherapeutic agent such as a thiosemicarbazone, but with no clear benefit.

Thus we conclude that the action of sulphones in leprosy is slow, sometimes very slow, but also very sure, and that the development in the bacilli of drug resistance is not a major factor in slowing up the response to sulphone treatment.

The Relapse Rate in Patients Discharged after Sulphone Treatment.

During these eight years, many different forms of treatment have been the subject of experiment in our Research Unit, and many of our patients have had more than one form of treatment. We here discuss only those who have had sulphone treatment only. Moreover our work with different sulphones has not shown conclusively the greater efficacy of one form of sulphone treatment over another, and the present report below makes no differentiation between the patients treated with different forms of sulphone.

We here consider only those who have continued treatment till the disease was considered arrested and inactive, the treatment had been stopped and the patient discharged. Every such case appearing on our records is included in the present study, with no selection and no omissions. The cases number **252.**

The criteria for cessation of treatment and discharge varied with the type of case. In lepromatous cases (all bacteriologically positive) treatment was continued until the disease had been clinically inactive, and until " smears " from the lesions had been found and remained bacteriologically negative for in most cases 12 months, with a *minimum* total period of treatment of 24 months; in non-lepromatous cases (nearly all tuberculoid and nearly all bacteriologically negative) six months clinical inactivity and a minimum treatment period in most cases of one year (later extended to 18 months).

Findings in lepromatous cases.

Lepromatous cases in this series number 162. They have varied widely in severity. Before treatment they were classified, on the results of bacterial examination of smears taken from the lesions, as:

Heavy infectious	(4+3+)	...	46
Moderate ,,	(2+)	...	52
Mild ,,	(1+)	...	64
			162

The period of treatment necessary to render the disease clinically inactive and the lesions bacteriologically negative varied between a few months (in a few very mild cases) and 74 months, the average being 28 months. The total period of treatment before discharge varied between 12 months and 82 months and averaged 41 months. The period that has elapsed since discharge varies between a few weeks and 61 months, and averages 22 months.

Of these 162 patients, 14 have only recently been discharged and are not yet due for re-examination. For the present purposes these may be ignored, and 148 remain.

Of these 148, 139 (94%) have been examined since discharge, some of them only once, most of them more than once, and some as many as nine times at intervals of several months.

The findings at the re-examinations of these 139 patients are here summarised.

No sign of relapse, clinical or bacteriological ...	124 cases
Slight *clinical* signs of relapse (neuritis only)	2 ,,
Slight *bacteriological* relapse (a few acid fast bacilli found in smears)	13 ,,
Clinical *and* bacteriological signs of relapse	Nil ,,
	139 ,,

Thus in not a single case has there been any really serious relapse.

In only 15 (10.8%) there was some evidence of relapse, in all cases slight.

In the two patients showing neuritis, this finding has been very recent. Treatment has been resumed and the neuritis has subsided in a few weeks, and no other signs have appeared.

Of the 13 showing a few bacilli in smears (often in the ear lobe), 3 were re-admitted for treatment and rapidly became negative. Of the other 10, two were referred elsewhere for treatment, and one of these, recently examined, was found negative 3 months later; the other has not been seen again.

The striking finding however is in the remaining 8 cases showing a few bacilli. They were sent away with no resumption of treatment, and told to report again later; six of them have done so, and five of the six are found negative on re-examination; the sixth still shows a few acid-fast bacilli in smears, but no other evidence of relapse.

Thus the significance of these findings of a few bacilli with no clinical evidence of relapse is not by any means clear. It may be that further studies will show that such "relapses" are of no serious importance.

Some further facts about these 15 cases of relapse may be of some interest.

The time that elapsed between the cessation of treatment and the detection of the relapse varied between 3 months and 23 months, and averaged only $7\frac{1}{2}$ months; in 12 of the 15 cases, the relapse occurred within one year. In not a single case has relapse been detected at more than two years after the cessation of treatment, although in some of the 148 cases the period of observation has been up to 5 years. Our findings, therefore, are that " relapse " occurs early or not at all. If this is confirmed, it is a most important finding, for it has been suggested that late relapse may present a real problem. Our findings are that, in Nigeria so far, late relapse has presented no problem at all.

The bacteriological status of these 15 cases before treatment started was:—

Heavy infections	...	...	6
Moderate infections	...	...	4
Slight infections ...	...	...	5

The period of treatment of these 15 cases had varied between 35 and 78 months, and it appears that their response to treatment had been rather slow. These findings indicate that relapse is not confined to the cases originally with heavy infection.

To sum up. Of 148 lepromatous cases treated with sulphones until the disease had been clinically inactive and smears negative for one year, discharged and later examined between 1 and 9 times for periods up to 5 years after discharge, serious relapse has not been seen in a single case. In 2 cases, leprous neuritis was found, although skin smears were negative. In 13 cases, a few bacilli were detected in smears but there were no clinical signs of relapse and, moreover, in these 13 cases, whether treatment was resumed or not, the smears later became negative in all but one of those re-examined later. All the relapses occurred early, usually within one year and all within two years of the cessation of treatment.

These results are extremely encouraging; in fact almost better than one had dared to hope.

Findings in tuberculoid cases.

The tuberculoid cases treated with sulphones only and then discharged number 90. The period of treatment in these cases has varied between 9 months and 34 months, and has averaged 20 months; the period since discharge varies between a few weeks and four years, and averages 22 months. Of the 90 cases, at the present time, 9 are not yet due for re-examination and are ignored. Of the remaining 81, 69 (85%) have been examined since discharge,

most of them more than once, and some up to 8 times, for periods up to 4 years.

In these 69 cases, 8 (11·6%) cases of reactivation of the disease have been seen. In all these 8 cases, the reactivation was clinical only; in none had smears from the lesions become positive.

Of these 8 relapses, 7 occurred between 3 and 12 months after the cessation of treatment; the other one was detected 28 months after the cessation of treatment.

Of the 8 cases of relapse, 3 occurred in a small group of patients who, for various reasons received less than 1 year's treatment; 3 occurred in a much larger group of patients who had received between 1 and 2 years' treatment; and 2 occurred in patients who had received between 2 and 2½ years' treatment. In the light of this experience, a period of at least 18 months to 2 years' treatment is recommended in such cases, although clinical inactivation of the disease is commonly seen within one year.

In all the eight cases, the relapse consisted in the recrudescence of clinical activity in the original lesions, sometimes with increase in size of these lesions, and sometimes with neuritis of the previously affected nerves. In none of these 8 cases did new lesions appear, although in similar cases not included in the present series, this has occasionally been seen.

In none of the 8 cases was the relapse serious, although it might have become serious if undetected or untreated. In all 8 cases, the resumption of sulphone treatment was followed by subsidence of the activity. Six of the 8 patients have again been discharged, while 2 are still completing their second course of treatment.

This incidence of relapse 8 (11·6%) out of 69 tuberculoid cases is unexpectedly high, for these tuberculoid cases of leprosy are relatively mild and are characterised by relative immunity to the infection. It is, however, noticeable that since we have increased the period of treatment in tuberculoid cases, relapses have been far fewer.

Discussion.

As previously stated, the only report of the late results of sulphone treatment available to me is that of Erickson.[5] He reported that of 77 lepromatous cases arrested by sulphone treatment, 33 had been re-examined and in 6 (18%) relapse had occurred, 3 of these relapses being clinical, and 3 subclinical, (smears from the lesions showed bacilli, but there was no definite clinical activity). Of these 6 cases of relapse, 5 patients had received intravenous promin for a period between 38 and 57 months, and one had received oral diasone for 18 months only.

Of the 33 cases re-examined, 11 had ceased treatment on discharge and of these 5 (45%) showed relapse; the remaining 22 had continued treatment after discharge and of these only 1 (4·5%) showed relapse.

In discussing these results, Erickson himself states:

> "The fact that relapses have occurred does not brand the sulphones as failures in the therapy of leprosy. In fact, it detracts very little, if any, from the reported value of these drugs in this relentless disease. Their ability to produce regression of leprous lesions and to keep the ravages of the disease in check cannot be discounted."
>
> "The figures given for the probability of relapse are tentative and, in the final analysis, may not be representative of what the true incidence of relapse eventually will be. Since the number of patients followed is small, a great deal of significance cannot be placed on the statistical results obtained. Also, the duration of follow-up has been short in some instances. A factor of selection may have entered into the calculations particularly with reference to the patients representing clinical relapse. Two of these patients had been discharged from the hospital and returned when skin lesions appeared. Since patients who develop visible evidences of the disease are, undoubtedly, more likely to return for examination than those who do not develop them, it may be that the three cases of clinical relapse here reported are the only ones that have developed among all of the patients so far having their disease arrested on the sulphones. Should this be the case, the probability of clinical relapse would be much less at the present stage."

These comments are much to the point. The three patients who had clinical relapse with visible lesions were perhaps, as Erickson states, the only ones in the group of 77. If this is so, the clinical relapse would be 4%, and the subclinical relapse rate, 3 out of 30, would be 10%, giving a total relapse rate of 14%. These figures are comparable with those here recorded.

There is no ignoring the fact, however, that Erickson's report is, on the whole, much less favourable than the present one, and causes for this difference must be sought.

The following points have to be considered:

(a). Our group of patients studied is much larger than that of Erickson (229 instead of 77), and moreover our re-examinations cover 90% of the discharged patients, whereas the figure for Erickson's group was only 44%. Our figures should be more reliable.

(b). The period of treatment of the two series of cases is not dissimilar, and the difference cannot be attributed to this factor. The form of sulphone treatment used, however, has differed widely. Most of Erickson's cases received promin intravenously, a form of treatment which is open to theoretical and practical objections (6). In our series, disubstituted sulphones given orally, and later dapsone (D.D.S.) given orally, have been used. We might be tempted to believe that our treatment is more effective than that used in Erickson's series, but there is no proof of this.

(c). It may be that in our Nigerian patients, the disease tends to be milder than in patients in the United States of America, and to respond more readily to chemotherapy, and also to relapse less readily. This idea is in accord with the experience of workers in different countries, who find that certain people tolerate sulphone treatment better and respond to it better than others. It may also be that our patients are treated earlier, and co-operate more fully in treatment and, therefore, respond better, and relapse less readily.

Of these possible factors, it appears that two may be important; our form of sulphone treatment may be more effective, and our patients may be peculiarly responsive to treatment.

In any case, we must maintain our sense of proportion. West Africa is a far more important focus of leprosy than the United States. We are justified in judging the efficacy of treatment of any disease by the response to treatment observed in patients in the great endemic foci of the disease.

Our experience in East Nigeria with sulphone treatment of leprosy on a very big scale has been far more favourable than that of Erickson in the United States. If it were found here, as he has reported in the U.S.A., that if treatment is stopped on discharge, the relapse rate may be as high as 45%, we should indeed be facing a serious problem. On the other hand, even if the relapse rate is only 10% as we have found it, Erickson's recommendation that, after discharge, treatment should be continued for a long period, and perhaps indefinitely, may still be worth consideration. Such continued treatment, if oral dapsone is used, can be carried out with very little trouble and at very low cost. All that is needed is the swallowing of a few tablets of dapsone every week; a tablet of 100 mg. may be swallowed daily; three or four similar tablets twice weekly, or even four or six tablets once weekly, at an annual cost of not more than four shillings per patient. This provides a simple and effective after treatment. Surely this is a very small price to pay for the maintenance of the arrest of leprosy.

SUMMARY AND CONCLUSIONS.

1. The late results of sulphone treatment of leprosy are studied from the patients and records of the Research Unit of the Leprosy Settlement, Uzuakoli, E. Nigeria.
2. As far as possible, the present condition (March, 1954) of every patient whose treatment started between March, 1946 and March, 1948 is studied, with the following findings:—
   (a) of 131 such cases on the records, 117 are available for analysis.

Disease inactive and smears negative. Discharged	88
Disease inactive and smears negative. Awaiting discharge	17
Disease inactive but smears still positive	12*
	117

(*Of these 12, only one has had eight years treatment, 4 seven years treatment, and 7 six years treatment.)

(b) Sulphone treatment is found to be very sure, but sometimes very slow in its action. It appears to produce arrest of the disease in every case, but may take a very long time to do it.

(c) Improvement up to a point, followed by deterioration, has not been seen, nor other finding indicating serious drug-resistance.

3. The relapse rate after the cessation of sulphone treatment is studied in the Research Unit patients with the following findings:

(a) Of 252 such patients discharged from the Settlement with instructions to return for re-examination, 23 are not yet due to return, and of the remaining 229, 208 (92%) have returned at least once and some up to 9 times, for periods up to 5 years.

(b) Of 148 discharged lepromatous cases, 139 (94%) have been re-examined, and of these 139, 15 (10.8%) have shown slight evidence of reactivation of the disease. No serious case of relapse has been seen.

(c) Of 81 discharged tuberculoid cases, 69 (85%) have returned for examination, and of these 69, 8 (11.6%) have shown signs of reactivation of the disease in the " tuberculoid " form. In none has the lepromatous form developed, and in none have positive " smears " been found.

(d) In both tuberculoid and lepromatous cases, reactivation occurred early, usually within one year, and almost always within two years of the cessation of treatment. Later relapse has not been seen.

(e) The cases of relapse with clinical manifestations rapidly responded to resumed treatment; and, in the rest, with only slightly positive smears, the smears have again become negative, in some cases with, but in some cases without, resumed treatment.

(f) Thus the relapses have been few, mild, and readily controlled. These findings are considered very satisfactory.

(g) The report of Erickson in the United States, of higher relapse rates, is considered, and also his recommendation of prolonged after-treatment as routine in discharged patients.

(h) The present findings in Nigeria hardly justify this routine after treatment; if however by further study it is shown to be advisable, it is so simple and economical that it should present no difficulty.

4. The findings of this study of the late results of sulphone treatment of leprosy reveal the main weakness of the treatment, namely the extreme slowness of its action; but also reveal its strong points, the sureness of its action and the permanence of results in most cases. These findings strengthen the view that is steadily gaining ground, that sulphone treatment constitutes a major revolution in the treatment of leprosy.

ACKNOWLEDGMENTS.

Thanks are due to many members of the staff of the Nigeria Leprosy Service for very valuable help given during the eight years covered by this study; particularly to Dr. T. F. Davey, O.B.E. who started the work, and to Miss F. McNulty and Mr. G. Okezie for laboratory work. To the patients, who have co-operated so well, thanks are also due.

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Later Note.

Since the above paper was written, I have seen the report of Wolcott & Ross (*International Journal of Leprosy* 1953, No. 4, pages 437-440) on "Exacerbations of leprosy during present day treatment." They report three cases, all lepromatous cases, treated, with marked improvement, and in two of the three cases, clinical inactivity and repeatedly negative smears. While treatment was still going on, there was severe reactivation of the disease, clinical and bacteriological.

In all these three cases sulphones had been given for a long time (apparently intravenous promin in all three cases, sometimes in "small amounts"), but other drugs were given, in one case isoniziad, and in the other, thiosemicarbazone, isoniazid, dihydrostreptomycin, P.A.S.; and in one case aureomycin and other medications were added.

They state that in recent years at Carville, Louisiana, U.S.A., a number of similar cases of exacerbation have been seen.

This experience is very different from mine in Nigeria. It is difficult to explain this difference.

The matter is briefly discussed above.

THE SIXTH INTERNATIONAL CONGRESS OF LEPROLOGY

MADRID, OCTOBER 3rd-11th, 1953

The Sixth International Congress of Leprology (this name was adopted by the local organising committee) was held in Madrid from October 3rd-11th, 1953. The arrangements for the Congress had been undertaken by a local organising committee, the General Secretary of which was Dr. Felix Contreras. The General Secretary of the International Leprosy Association, Dr. Ernest Muir, had visited Madrid twice, and in between visits had done much to help in the organisation of the Congress. During the congress the committee's responsibility was shared by the Officers, Executive Committee and General Council.

Three hundred and thirty-seven persons registered as members of the Congress, and there were also many " adherents ". Fifty-one countries were represented, Spain by 117, Brazil by 33, the United States by 25, France and territories by 25, Argentina by 19, Germany by 14, Britain and overseas territories 21, and other countries by smaller numbers. No communist country was represented.

One great practical difficulty was encountered in dealing with the very large number of papers submitted, totalling 227. It had been announced that no worker could submit more than two papers (and only a few exceeded their ration). Interpretation arrangements were available in only one room; multiple simultaneous sessions were not possible. It was therefore decided that no one worker would read more than one paper. The sessions were increased to eight, but even so the time allowed for presentation of each paper was often inadequate. Translators experienced much difficulty because many speakers spoke too fast; it was therefore often difficult to understand the papers presented; such difficulties are not uncommon in such international gatherings. They are mitigated by the fact that all papers read are, or should be, available in abstract before they are read.

The attendance at some of the sessions of the Congress was poor. There were several reasons for this: much work of the Congress had to go on during sessions, for example, office and administrative work, and sometimes technical committees; our Spanish hosts had arranged officially and unofficially many social events of a most attractive nature, and some overlapping of these with the working sessions was unavoidable: the difficulties mentioned above reduced the interest of some sessions.

The technical committees appointed numbered five, and the meetings of these committees provided much valuable sharing of ideas and experience. The proceedings of the Congress included the following as the main items of work:— a preliminary meeting of the General Council to approve the arrangements, eight sessions of the Congress for the reading and discussion of papers, a varying number of meetings of the five sub-committees, a final meeting of the Congress Council, the final plenary session of the Congress, and a formal closing session.

At the final plenary session, the reports of the five sub-committees were presented, discussed, and voted on. The reports of the committees on Therapy, Immunology and Social Aspects were adopted with little or no discussion. The report of the committee on Epidemiology and Control had, in the opinion of the General Council, laid more emphasis on B.C.G. vaccination in control than was justified by evidence, and the General Council had, under the rules of procedure of the Congress, suggested that the Report be modified in this respect. The proposal however was not approved by the Plenary Session, and the report was adopted as presented.

The Congress left one with mixed feelings. The social side was magnificent, and was greatly enjoyed by those who were free because not engaged in congress business. The opportunity of meeting workers from so many countries and sharing views and experience was greatly welcomed by all. The more serious aspects of the Congress were less satisfactory. The difficulty of the large numbers of papers and their proper presentation and discussion was insuperable. The work of the sub-committees was done under great difficulties, at odd times and all hours, and often the report was drafted against pressure of time. Free discussion of the reports at the final plenary session had to be curtailed. These conditions are not conducive to good work.

The present writer has long held the view that International Leprosy Congresses should be run on lines quite different from in the past, and has made suggestions on the matter. Experience at Madrid has strengthened his view, that this is not the best kind of congress, and that the whole matter should be thoroughly explored long before the next Congress. J.L.

TECHNICAL REPORTS

We here reprint (from the International Journal of Leprosy, Vol. 21, No. 4, Oct. Dec. 1953) the reports of the Technical Committees of the Madrid Congress, as adopted by the plenary session of the Congress.

CLASSIFICATION[1]

The criteria which bear on the classification of leprosy cases are: (1) clinical, (2) bacteriological, (3) immunological, and (4) histopathological. Existing systems of classification differ with respect to the priority given certain of these criteria.

The Committee agrees unanimously that the basic criteria of primary classification should be clinical, comprising the morphology of the skin lesions and the neurological manifestations. Indispensable in connection with the clinical examination is the bacteriological criterion, involving examination of smears from skin lesions and the nasal mucosa.

In the study of cases full use should be made of the immunological criterion (the lepromin test) and of the histopathology of the lesions. These factors are of value in the determination of types, and may be essential in the determination of sub-groups.

The histological examination, though important in the diagnosis of the form of leprosy and consequently in connection with prognosis, should not govern the primary classification, except when, as may happen, it definitely indicates the clinical classification of the case to have been in error. In such instances—if the lepromin reaction is in agreement with the histologic findings—the case should be reclassified.

Cases should be classified according to findings at the time of the examination. They may or may not present evidence, by history or by objective stigmata, of a previous form or phase of evolution, and sometimes these features are significant with respect to present classification.[2] The evidence obtainable may indicate a likelihood of change to another form or phase in the future evolution of the disease, but that factor does not affect the determination of form (as to type or group) until such a change actually occurs.

The Committee considers that this system of classification offers every possibility for further progress.

PRIMARY CLASSIFICATION

The Committee recommends that two distinct *types* of leprosy,

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[1] The Committee on Classification was composed as follows: Dr. H. W. Wade, *chairman*, Dr. José Gay Prietro, *vice-chairman*, Dr. Martín Vegas, *secretary*, and Drs. G. Basombrío, R. G. Cochrane, V. R. Khanolkar, Kanehito Kitamura, Francisco Lapatí, and Francisco E. Rabello, *members*; also, Dr. Harry L. Arnold, Jr., *co-opted member*.

[2] For example, it may be known, or be evident from existing stigmata, that a case presenting only simple macules was previously tuberculoid. Such a case should be classified as "residual tuberculoid" and not as "indeterminate."

lepromatous and tuberculoid, be recognized, thus maintaining the concept of polarity. It also recommends that two *groups* be recognized, indeterminate and borderline (dimorphous).

The following definitions are offered:

Type connotes clinically and biologically stereotyped features, characterized by marked stability and mutual incompatibility.

Group connotes less distinctive or positive characteristics, less stability, and less certainty with respect to evolution.

Variety connotes a subdivision of a type or group.

PROPOSED TYPES, GROUPS AND VARIETIES

Lepromatous type (L)
- Macular
- Diffuse
- Infiltrated
- Nodular
- Neuritic, pure (?) [3]

Tuberculoid type (T)
- Macular
- Minor tuberculoid (micropapuloid, etc.)
- Major tuberculoid (plaques, annular lesions, etc.)
- Neuritic, pure.

Indeterminate group (I)
- Macular
- Neuritic, pure

Borderline (dimorphous) (B)
- Infiltrated
- (Others?) [4]

LEPROMATOUS TYPE (L)

A malign type, especially stable;[5] strongly positive on bacteriological examination; presenting more or less infiltrated skin lesions; negative to lepromin. The peripheral nerve trunks become manifestly involved as the disease progresses, habitually in symmetrical fashion and often with neural sequelae in advanced stages.

TUBERCULOID TYPE (T)

Usually benign; stable; generally negative on bacteriological examination; presenting in most cases erythematous skin lesions which are elevated marginally or more extensively; positive to lepromin.

Sequelae of peripheral nerve trunk involvement may develop in a certain proportion of cases, and this may give rise to serious and disabling deformity. This frequently appears to occur as a result of extension from or through cutaneous nerve branches, rather than of systemic dissemination, and consequently it is often asymmetric and unilateral.

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3 Cases of this variety have been observed by some workers, but have not as yet been reported in the literature.

4 See addendum by Drs. Khanolkar and Cochrane.

5 The word "stable" implies stability as regards the type, not as regards the severity of the disease.

Tuberculoid leprosy should be subdivided as follows:

Macular tuberculoid (Tm). These cases present macules with clear-cut and definite margins, the surface generally smooth and dry, invariably with some loss of cutaneous sensibility; almost always negative on bacteriological examination, or with at most only a few bacilli.

Minor tuberculoid (micropapuloid, etc.) (Tt). Skin lesions are only slightly to moderately elevated, often only at the margin or even a part of the margin, usually with irregularity of the surface. The condition tends to be relatively superficial, and palpable enlargement of cutaneous nerves associated with the lesions is infrequent.

Major tuberculoid (plaques, annular lesions, etc.) (TT). Skin lesions, often smooth of surface, are more markedly elevated and thickened than those of the minor variety, the affected zone usually broader; the more recent lesions may show only partial central recession or no recession. Because of the degree of the condition in the deeper levels of the skin, manifest extension in the associated cutaneous nerves is relatively frequent and marked.

INDETERMINATE GROUP (I)

A benign form, relatively unstable; seldom bacteriologically positive; presenting flat skin lesions which may be hypopigmented or erythematous; the reaction to lepromin negative or positive. Neuritic manifestations, more or less extensive, may develop in cases which have persisted as of this group for long periods. The indeterminate group consists essentially of the " simple macular " cases. These cases may evolve towards the lepromatous type or the tuberculoid type, or may remain unchanged indefinitely.

BORDERLINE (DIMORPHOUS) GROUP (B)

A malign form, very unstable; almost always strongly positive on bacteriological examination; the lepromin reaction generally negative. Such cases may arise from the tuberculoid type as a result of repeated reactions, and sometimes they evolve to the lepromatous type. The nasal mucosa often remains bacteriologically negative, even when the skin lesions are strongly positive.

The skin lesions are usually seen as plaques, bands, nodules, etc., with a regional distribution similar to that of lepromatous leprosy, except for conspicuous asymmetry. The ear lobes are likely to present the appearance of lepromatous infiltration. The lesions frequently have a soft or succulent appearance, and peripherally they slope away from the centre and do not present the clear-cut, well-defined margins seen in the tuberculoid type; they are therefore liable to be mistaken for lepromas. The surface of

the lesions is generally smooth, with a shiny appearance and a violaceous hue, sometimes (in light skins) with a brownish (sepia) background.

REACTIONAL PHASES

All forms of leprosy may go through phases of reactivation or reaction. We would particularly draw attention to three main reactional phases of leprosy, as follows:

Reactional lepromatous leprosy.—Two forms must be distinguished:

(1) Lepra reaction (of which there may be two or more varieties) consists essentially of the aggravation of pre-existing skin lesions, usually with fever and extension of the lepromatous process.

(2) Erythema nodosum leprosum is characterized by the appearance of erythematous nodular skin lesions, accompanied at times by fever, and has as a rule a favourable prognosis.

We would further draw attention to the special condition known as the " Lucio phenomenon " or " erythema necrotisans," occurring only in diffuse lepromatous leprosy and more particularly in Central America.

Reactional tuberculoid leprosy.—Infiltrated lesions of active, succulent appearance, without central retrogression, develop abruptly from major tuberculoid lesions or from lesions of lesser degree (minor tuberculoid or even indeterminate), or on sites not previously involved. In some cases more or less numerous and widely scattered small metastic nodules may appear. The lesions of the peripheral trunk nerves may become marked, and necrosis and even abscess formation may occur. On bacteriological examination, although the cutaneous lesions are found to be positive, sometimes strongly so, the nasal mucosa frequently remains negative. During the reaction the response to lepromin may decrease in intensity. Fever and constitutional symptoms do not ordinarily occur.

Reactional borderline (dimorphous) leprosy.—In reactional borderline cases the lesions show extreme oedema, erythema and desquamation. The reaction frequently extends to nerves, and marked nerve pain and dysfunction develop. The skin lesions, during this phase, may ulcerate superficially, or sometimes widely and deeply; and the skin is acutely tender. Bacteriologically the lesions are strongly positive. The lepromin reaction is usually negative.

ADDITIONAL NOTE

1. The classifying factor is mainly clinical, but it is advisable for workers to give consideration to the immunological and histo-

pathological criteria. These factors may decisively influence the placing of a case in a particular type or group.

2. Cases of the lepromatous or tuberculoid types with only recessive or residual lesions remain in their respective types. Such cases may be described as recessive or residual, and these terms should be added to the description of the main types, e.g., L(res), T(res), etc.

ADDENDA

DR. WADE registered a dissenting opinion regarding the recognition of a "macular" variety of the tuberculoid type, on the following grounds:

For classification to be understandable to all serious workers in leprosy, and not merely to the expert specialist, the line of demarcation between the tuberculoid type and the group or groups which present "simple" flat macules should be as distinct as possible. The distinction must necessarily be based on clinical aspects, primarily the morphology of the lesions, elevation and usually certain other features being characteristic of the lesser tuberculoid cases. In his opinion the inclusion, in this type, of a variety of simple macular cases, commonly known in the past as "maculo-anaesthetic," would cause much confusion. This same proposal was made by the classification committee of the Havana Congress, in that part of the report which was rejected by the Congress in plenary session.

Regarding the argument that a great majority of the lesions which it is proposed to call "macular tuberculoid" will, if active, show histologically some degree of tuberculoid change if it is sought with sufficient care, it is to be said that that change is not outwardly evident because of the relatively low degree of tissue reactivity. In keeping with that circumstance, cases with such lesions are as a rule less responsive to treatment than are frank tuberculoid cases.

Incidentally, the creation of a "macular" tuberculoid variety would increase confusion in terminology. All of the skin lesions of tuberculoid leprosy are commonly referred to by many leprologists as "macules," and the Japanese leprologists use the term "lepra maculosa" for the tuberculoid form as a whole.

For these reasons he adheres primarily to the definitions of the tuberculoid type and the indeterminate form adopted by the Expert Committee on Leprosy of the WHO, the pertinent parts of which are as follows:

(1) Cases of the indeterminate group present "flat skin lesions." The group "consists essentially of the 'simple macular' cases and comprises those cases previously known as 'maculo-anaesthetic'."

(2) Cases of the tuberculoid group present "erythematous lesions which are elevated, marginally or more extensively. . . ." and in the minor variety the "skin lesions are only slightly to moderately elevated, often at the margin or even a part of the margin, usually with irregularity of the surface."

Agreeing fully that those cases which have become established in the "maculo-anaesthetic" form should not be retained in the "indeterminate" group, he holds that they should be recognized as a distinct "group," a view which is in accord with the conclusions of a special classification committee recently set up by the Indian Association of Leprologists.

DRS. KHANOLKAR and COCHRANE hold that there exist macular dimorphous lesions which have clinical, bacteriological, immunological and histological features which justify their inclusion in the borderline (dimorphous) group. They further are of the opinion that, if a careful study is made, a pure neuritic form of the borderline (dimorphous) group could be established.

The following is a description of what is considered a dimorphous macule:

These macules show, clinically, characteristics of both the tuberculoid and lepromatous types. Their distribution is that of lepromatous leprosy; the margin of the lesion is less definite than that of the tuberculoid macular lesion, but not so vague as that of the lepromatous macule; the surface

tends to be dry and may show a wrinkled or creased appearance. On careful examination some loss of cutaneous sensibility can be elicited.

NOTE: In compiling this classification, the Committee is indebted to the report of the WHO Expert Committee on Leprosy, kindly supplied by Dr. Mario Giaquinto.

TREATMENT [1]

GENERAL

In the report of the Fifth International Leprosy Congress, held in Havana in 1948, sulphone treatment of leprosy was discussed and very favourable results were recorded. In the five years that have passed since then the use of the earlier forms of sulphone treatment have been continued and extended, new forms of sulphone treatment have been developed and very widely applied, and much more information is now available. In general, the value of the sulphones in the treatment of all forms of leprosy has been confirmed, but at the same time certain limitations of the treatment have become more apparent. In the present report an attempt is made to assess the present position.

During these five years, new chemotherapeutic agents and antibiotics originally developed for use in tuberculosis have been used in leprosy. The results of such trials are here considered, and a preliminary assessment of them is attempted.

SULPHONE TREATMENT

The Committee is agreed that the sulphone drugs have been proved by twelve years of clinical trials to be more effective than any treatment previously used. At present they must be considered the basic treatment of all forms of leprosy.

Forms of sulphone treatment.—A variety of mono- and di-substituted forms of sulphone drugs have been prepared and tried clinically since 1941, but there is no clear indication that any one compound is more effective than any other. The parent drug, 4,4'-diaminodiphenyl sulphone (DDS), once found too toxic for use in man, has been used extensively since 1948 in a much reduced dosage, and is safe and as effective as the substituted compounds. The smallness of the dose of D.D.S. makes it much less expensive to use than the compounds.

The tolerance of different people and different races to sulphones appears to vary. The standard dose of D.D.S. for adults should not be less than 300 mg a week, and not more than 1,200 mg. a

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1 The Committee on Treatment was composed as follows: Dr. José N. Rodriguez, *chairman*, Dr. Lauro de Souza Lima, *vice-chairman*, Dr. José Gómez Orbaneja, *secretary*, and Drs. A. R. Davison, H. Floch, John Lowe, Salomón Schujman, M. Santos Silva, and Rolla R. Walcott, *members*.

week. The drug can be given daily, on alternate days, twice weekly, or weekly. It can be given by mouth or by intramuscular injection. The very large number of complex sulphones now in use makes it impossible to give here details of dosages. The dosages of some of them are detailed in the proceedings of the Havana Congress.

Induction and maintenance.—Gradual induction of sulphone treatment is of paramount importance. Even in robust patients the initial dose should be about one-fourth of the standard, and the gradual increase to the standard should take six to eight weeks. In debilitated patients the initial dose should be lower and the increase slower. Regular treatment must be maintained, but some workers find brief rest periods desirable. Increase of the dosage above those generally accepted may increase toxicity and does not improve results. Attempts to improve treatment by giving sulphones in combination with other therapeutic agents have been made, without conclusive results.

Toxicity and complications.—The following toxic effects of sulphone therapy have been recorded: allergic dermatitis, psychosis, hepatitis, anaemia and anorexia. Of these, dermatitis and psychosis are the most serious. The frequency and severity of these conditions vary widely in different parts of the world.

Various complications may arise during sulphone treatment, among which are erythema nodosum leprosum, neuritis, eye complications and other sub-acute manifestations.

The above toxic effects and complications necessitate careful regulation of the treatment to the individual patient, stoppage of treatment for a period, or occasionally a change to another form of treatment.

Mode of action.—The mode of action of sulphone drugs in leprosy is not clear. They are apparently not bacteriological; they may be bacteriostatic.

Results.—The *early results* of sulphone treatment as described below are recorded by almost all workers. Most patients show decided clinical improvement within a period of months after the treatment is begun. There is usually an improvement of general health with increased appetite, body weight and strength, which is accompanied by a decrease of distressing symptoms due to the disease. Specific lesions usually recede. Bacteriological improvement is slower than symptomatic and clinical improvement.

Experience of the *later phases* and *end results* of treatment varies widely. In some centres, after prolonged treatment, clinical and bacteriological arrest of the disease has been attained in a high

proportion of cases, and has been maintained over a period of years. In other centres, arrest has occurred in only a relatively small proportion of cases, and relapse has not been uncommon; such findings have led to the suggestion, that after long treatment, sulphone resistance may develop in the bacilli. There is no strong evidence for or against this idea.

The type and the duration of the disease before the institution of treatment vary widely in different centres, and this has an influence on the duration of treatment needed to arrest the disease, and on the end results of treatment.

Further, it is generally accepted that the severity of leprosy differs in different races, and it seems likely that the response to treatment will vary correspondingly.

These two factors may help to explain the disparity of results recorded in different centres.

Management of "arrested" cases.—Various observations indicate that arrested cases are not completely freed of leprosy bacilli, and that reactivation of the disease is therefore not unlikely. Continuing observation is indicated in all "arrested" cases in order that any reactivation may be detected as soon as possible.

The after-treatment of "arrested" cases may reduce the relapse rate, and, with oral administration of the drug after-treatment can be very simple. It is a recommended procedure in those areas where it is practicable.

OTHER THERAPEUTIC AGENTS

(a) Chaulmoogra oil and derivatives.—Nearly all workers have abandoned the use of chaulmoogra oil in favour of sulphone treatment. A few experienced workers continue to use chaulmoogra oil as well as sulphones.

(b) Thiosemicarbazones.—Para-acetamidobenzaldehyde thiosemicarbazone (TB-1) is the only one of these drugs which has been widely used. Reports of its value in leprosy vary greatly. A few workers have found it equal to sulphones; most find it less effective.

Serious toxic effects may be seen, especially in the first few weeks of treatment, agranulocytosis, hepatitis, and severe anaemia being the most important.

We consider that the dose should not exceed 300 mg. a day in the adult. Some workers find even this dose too high, and use a maximum of 150 or 200 mg.

At present, thiosemicarbazone is recommended only as a *useful alternative treatment* for those patients who do not tolerate sulphones, or who fail to respond to sulphones. Further work is

needed before a definite appraisal of this drug in leprosy can be made.

(c) Isonicotinyl hydrazide (INH).—Nearly all workers feel that INH has little beneficial action in human leprosy. Its use in combination with other agents may be worth study.

(d) ACTH and cortisone.—There is wide agreement that intramuscular injections of these hormones have a striking effect in relieving the acute and sub-acute manifestations of leprosy, and that small doses may be effective. There is, however, a wide difference of opinion regarding the late results of this hormone treatment in leprosy. Some workers find that the cessation of hormone treatment is frequently followed by the recurrence of the acute manifestations, and by an increase in the underlying disease; they think that the use of these hormones should if possible be avoided in the presence of leprous or any other infection. Other workers have not encountered this difficulty and do not share this view.

The local use of cortisone for eye complications by eye-drops or by subconjunctival injection is not open to this objection, and is often of great value.

Short courses of injections of ACTH or cortisone have been reported to be of great value in the treatment of serious toxic and allergic reactions to drugs, e.g. sulphones and thiosemicarbazone.

(e) Streptomycin.—Trials of this antibiotic have been made and are in progress. As yet no striking results have been recorded.

Because of its lower toxicity dihydrostreptomycin has been found preferable to ordinary streptomycin. The early response of the disease to streptomycin has tended to be slower than to sulphones. Later, after nearly one year, the difference has been slight.

The dose recommended, 1 gramme three times a week, has been given for one year without measurable damage to the eighth cranial nerve.

Some workers have found streptomycin to be of some value in the relief of the acute manifestations of leprosy.

The use of streptomycin in leprosy must still be regarded as experimental.

(f) P.A.S.—This drug has been tried in leprosy, alone and in combination with other agents. No striking results have been observed.

PHYSICAL THERAPY AND SURGERY

While chemotherapy has greatly improved the general outlook in the treatment of leprosy, its action on trophic lesions produced

by nerve involvement or nerve destruction is often slight. In dealing with these conditions affecting the hands, the feet, and sometimes the face, physiotherapy, surgery and orthopaedics have a place, which however has not yet been fully defined. A more thorough study of these matters is urgently needed.

Physiotherapy may ameliorate some of the symptoms caused by peripheral neuritis, and may be a valuable aid in the post-operative care of patients undergoing surgical treatment.

Reconstructive surgery is most beneficial in patients whose disease is clinically quiescent or arrested. Tendon transplantations, arthrodeses, and other surgical procedures may improve the function of contracted hands. Amputations may be needed, particularly in the feet. Successful surgery of this nature may contribute much to the rehabilitation of patients in whom the disease has become arrested.

THERAPY RESEARCH

The favourable results of the present methods of chemotherapy of leprosy should not be allowed to obscure the great need for new chemotherapeutic agents acting with greater speed and efficacy, or to handicap research directed towards the establishment of more effective treatment.

There is urgent need for large scale, carefully planned and accurately conducted therapeutic trials of certain agents already available, and of new agents as they become available. Such trails should include studies of possible therapeutic agents given singly and in combination. In view of the rather wide differences of results of chemotherapy in people of different races, therapeutic trials should be made in different centres and in different countries.

The response of a suitable group of cases of leprosy to the well-established sulphone drugs may be used as the control in experiments designed to assess the value of newer drugs.

ADDENDUM

DR. SCHUJMAN holds that some authors who have studied comparatively the effects of both chaulmoogra and the sulphones maintain that chaulmoogra oil, if given in sufficient doses (15 to 25 c.c. weekly) is sufficiently active in all forms of leprosy to justify its retention in the therapeutic armamentarium.

IMMUNOLOGY

For the first time this subject is included among the themes of an international congress of leprology. The decision to do this results from the importance now ascribed to the lepromin reaction, after many years of experience, and also from the results obtained in certain countries with B.C.G. which may open up new horizons in the prophylaxis of this disease.

THE LEPROMIN REACTION

The use of the lepromin reaction as an index of the degree of resistance to *Mycobacterium leprae* is constantly increasing. It offers a useful element in respect to prognosis and classification of cases of leprosy, and consequently its use in practice is recommended.

Antigens.—For the preparation of the antigen the Committee recommends the method which fulfills most closely the following requirements: (*a*) susceptibility of standardization; (*b*) maximal utilization of the bacillary element of the material used; and (*c*) the greatest simplicity of preparation.

The method of Dharmendra gives an antigen which can be standardized with minimal loss of bacilli. On the other hand, the late reaction is weaker than with other lepromins, perhaps because the chloroform and ether employed in its preparation modify the composition of the bacilli.

The method of Fernández and Olmos Castro gives a standardized antigen with bacilli very little changed in their composition, but it has the disadvantage that a great many bacilli are wasted in its preparation.

The Mitsuda-Hayashi method, in spite of the fact that it gives a cruder antigen which cannot be standardized, is most widely used because of the simplicity of its preparation and its practical efficacy.

With these considerations in mind, the Committee recommends as preferable: (*a*) for routine work, the Mitsuda-Hayashi antigen as modified by Wade; (*b*) for investigations, the more purified and standardizable antigens, the method of preparation of which should always be specified.

Because of the increasing scarcity of material for the preparation of lepromin, the Committee recommends increased studies of new methods and refined techniques of preparation (see appendix), and also the use of higher dilutions of the antigen. The use of visceral lepromin as suggested by Campos should also be investigated further.

Finally, the Committee suggests that it would be desirable to ask central laboratories, with facilities for the purpose, to undertake the preparation of the antigen for distribution to those who may need it. An antigen of the Mitsuda type will be the more uniform, the more numerous the lesions from which it is made.

READING OF THE LEPROMIN REACTION

The intradermal injection of lepromin provokes, in those who react positively, a double response: (*a*) an early reaction in 24 to

48 hours—the reaction of Fernández; (*b*) a delayed reaction read at about the fourth week—the reaction of Mitsuda.

The Early Reaction.—This consists of an erythematous infiltrated lesion, sometimes evident twelve hours after the injection, the aspect and evolution of which resembles the reactions of the tuberculin type. It reaches its maximum after 24 to 48 hours, and begins to diminish after 72 hours. In strongly positive cases it persists for a longer time in the form of a dark halo surrounding the late nodule.

In the reading of the reaction the only element of importance is the infiltration. Reactions which present only erythema should be considered doubtful or negative, and also reactions which appear very early and regress or disappear before 48 hours. A sharp margin of ameboid configuration is peculiar to very strong positive reactions.

It is recommended that the results should be read after 48 hours, conforming to the following criteria:

Negative (—): Absence of reaction, or erythema without infiltration, or erythema with infiltration less than 5 mm. in diameter.

Doubtful (±): An erythematous-infiltrated reaction with infiltration more than 5 mm. and less than 10 mm. in diameter.

Weak positive (+): An erythematous-infiltrated reaction with infiltration more than 10 mm. and less than 15 mm. in diameter.

Moderate positive (++): An erythematous-infiltrated reaction with infiltration more than 15 mm. and less than 20 mm. in diameter.

Strong positive (+++): An erythematous infiltrated reaction with infiltration more than 20 mm. in diameter.

The Delayed Reaction.—This consists of a nodular infiltration which begins after the first week after the injection, reaches its maximum about the fourth week, and later regresses, frequently leaving atrophy or a scar. Intensely strong reactions may result in ulceration. Sometimes the evolution is accelerated and reaches its peak before the third week, while at other times it is delayed, reaching its peak after the fourth week. In negative or doubtful cases it may be well to make later readings up to 60 days.

The criterion of reading should be based not only on the size of the infiltration, but also on its appearance and evolution.

Negative (=): Absence of all local reaction between the first and fourth weeks.

Doubtful (±): Slight infiltration, difficult to detect and less than 3 mm. at the point of inoculation.

Weak positive (+): Frank infiltration between 3 and 5 mm. in diameter.

Moderate positive (++): Nodular infiltration larger than 5 mm. in diameter.

Strong positive (+++): When the infiltration undergoes ulceration.

INTERPRETATION OF THE RESULTS

A positive lepromin reaction is regarded as an expression of

a certain amount of resistance to *Mycobacterium leprae*, directly proportionate to the degree of positivity.[1]

A negative lepromin reaction is interpreted as follows:

(*a*) In patients with leprosy, and contacts living with open cases, it is generally regarded as a sign of deficient resistance.

(*b*) In healthy individuals not contaminated with leprosy, it is without significance.

B.C.G. AND LEPROMIN REACTION

Studies of conversion of lepromin negative individuals to positive by means of B.C.G. have been widely undertaken in recent times. There is no doubt that if experience shows that this artificially induced change is of value in immunity, this will have a decisive influence on the future orientation of the prophylaxis of leprosy. The Committee is in agreement in accepting:

(1) Healthy people with positive lepromin reaction, not artificially produced, frequently present a state of biological resistance to *Mycobacterium leprae*.

(2) In leprosy patients, a positive lepromin reaction, not artificially produced, gives, from the biological point of view, a favourable prognosis.

(3) Spontaneous or natural conversion of the reaction takes place in a large proportion of cases.

(4) The administration of B.C.G. to healthy individuals who are negative to lepromin, causes a change of the reaction in a large proportion of cases.

(5 The administration of B.C.G. in the usual doses by mouth is free from risk, even in allergic individuals.

The question of whether or not a positive lepromin reaction artificially induced by B.C.G. indicates immunity is being studied, and as yet no conclusive statement can be made regarding the matter.

The Committee recommends that experimentation be intensified to determine the value which this vaccine may have, and also that wider investigation be made with a view to finding other procedures equally capable of converting the lepromin reaction.

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1 It is certain that intense reactivity to lepromin reflects biologically a favourable prognosis. This state of hypersensitivity may, in certain cases, result in clinical changes prejudicial to the patient (atrophies, mutilations, reactional occurrences, etc.).

APPENDIX

The following description of the improved (Wade) technique of preparation of the Mitsuda-Hayashi antigen, referred to in the text of this report, is taken verbatim from the report of the W.H.O. Expert Committee on Leprosy (W.H.O. Technical Reports Series No. 71, September 1953).

(1) For each batch of lepromin, lesion-tissue from several cases should be used, and reliance should not be placed alone on a tissue such as the ear lobe. The purpose of this "pooling" of material is to compensate for possible antigenic deficiencies of material from one or more cases by inclusion of material from others which may be more favourable.

(2) Each specimen used should be incised and a bacteriological smear examined, to ensure that only those which contain abundant bacilli will be used. Those poor in bacilli should be discarded.

(3) All tissue extraneous to the actual lesion mass should be trimmed off and discarded. This includes subcutaneous fat and loose connective tissue, as well as the epidermis if the lesion is a cutaneous nodule or infiltration, and the skin itself if it is removed with a subcutaneous nodule and is not involved in the lesion.

(4) It is probably preferable to weigh the tissues to be used before they are heated. (A material loss of weight occurs in the heating, whether that be done by boiling or by autoclaving, and whether it be done in saline solution or without it.)

(5) The trimmed tissue is heated either at boiling temperature or by autoclaving. The latter form of sterilization is to be used if the tissue is to be shipped to a distant laboratory for processing.

(6) The heated material is ground fine in a mortar with gradual addition of saline up to 20 ml per gram of tissue.

(7) The material is then filtered. Filtration is best done through a single layer of the finest mesh bolting cloth of silk, or preferably of nylon, the latter having no capillary attraction for water. (This process avoids the loss of a great deal of tissue suspension which occurs when highly absorbent multiple layer cotton gauze filters are used.) The nylon fabric is applied, provision being made for a pouch, to a wire ring made to fit the funnel to be used. The suspension is worked through by gentle scraping with a spatula. The nylon filter, properly cleaned, can be sterilized and used repeatedly.

(8) The residue left on the filter may be returned to the mortar, reground for some minutes, suspended in fresh saline, and put back into the same filter. (In this way 20 ml of saline per gram of tissue can be used in the first instance and 10 ml per gram in the second instance, thus obtaining 50% more of the final preparation than when the tissue pulp is not reground.)

(9) 0·5% of phenol is added to the filtered suspension which is then distributed in the desired containers, which are sealed and reheated to ensure sterility, although asepsis is practiced throughout.

EPIDEMIOLOGY AND CONTROL

The Fifth International Congress of Leprosy, held in Havana in 1948, dealt in detail with the subjects of epidemiology and control of leprosy in the light of knowledge existing at that time. The present report gives emphasis to certain new facts which have been brought to light in the past five years, namely:

1. The influence that the medicaments have with respect to control.

2. The promising results which have recently been obtained with the lepromin reaction induced by B.C.G.

EPIDEMIOLOGY

The Committee emphasizes, for those countries with endemic leprosy, the importance of obtaining more extensive data on the prevalence of the disease. The determination of prevalence, in highly populated countries, is to be accomplished by means of surveys, which should meet the following conditions:

(*a*) The groups studied should be relatively large, and carefully selected;

(*b*) Consideration should be given to the socio-economic and climatic factors, and to others including race, sex, and age.

(*c*) The proportions of the types and groups among the cases encountered should be determined.

To determine the trend of disease, such surveys should be made as frequently as possible, the intervals not exceeding ten years.

We emphasize the concept that the evaluation of control measures should be based on the results of such epidemiological studies.

CONTROL

The modern anti-leprosy campaign is based upon the following points:

1. *Education and health propaganda:*

(*a*) The training of leprologists by means of special courses of instruction.

(*b*) The training of health officers, who should participate, in every way possible, in the campaign against leprosy.

(*c*) The instruction of general practitioners.

(*d*) The introduction or development in the curricula of medical schools of adequate courses of instruction in modern leprology.

(*e*) The proper preparation of auxiliary health personnel.

(*f*) Health propaganda, which should be carried out by specialized organizations having as their ultimate aim the discovery, as completely as possible, of the cases of the indeterminate group, which form the matrix of the endemic condition.

2. *Protection and control of contracts:*

A. Protection:

(*a*) Induction of lepromin reactivity by means of B.C.G.[1]

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[1] The General Council of the Congress proposed that this sentence be struck out, holding that the use of B.C.G. is still in the experimental stage and that as yet there is no adequate evidence to justify the indicated view that it is an established measure of prophylaxis. The final plenary session, however, voted for the retention of the statement.

(*b*) Preventive treatment of contacts beyond the age of ten years who remain lepromin negative in spite of B.C.G. vaccination. The possibility of applying this measure to children of younger age should be considered.

B. Control:

This should be effected with the following orientation:

(*a*) Lepromin-positive contacts of indeterminate and quiescent tuberculoid cases do not require surveillance.

(*b*) Lepromin-positive contacts of lepromatous cases require periodical, although not frequent, surveillance.

(*c*) Lepromin-negative contacts should be observed periodically, as frequently as possible.

3. *Out-patient treatment* of tuberculoid and indeterminate cases, and also lepromatous cases presenting few lesions with scanty bacilli, and which are susceptible of being made negative within a short period of time.

4. *Selective isolation* of contagious cases. The period of hospitalization should be sufficiently long to obtain clinical regression and bacteriological negativization in examinations made periodically, taking into account the conditions prevailing in each country. Once this has been achieved, the patient can be transferred to a dispensary, where he will continue to be under regular observation and treatment.

5. *Scientific investigation:* This activity is of special importance because of the knowledge to be derived from it regarding the prevalence and incidence and the methods of control.

6. *Social assistance:* This should include the material and moral assistance to the children and other relatives of the patients, until he is completely rehabilitated and able to return to his work.

To accomplish these objectives of the modern anti-leprosy campaign, the following institutions should be provided:

1. *Sanitarium:* This institution should have as its principal objective the recovery of the physical and moral health of the patients in the broadest sense of the term.

2. *Urban or transient hospital:* Such a hospital may function either as an independent unit, or as an auxiliary of the dispensary or of a general hospital.

3. *Dispensary:* This entity should play a preponderant and dynamic role among the agencies of the anti-leprosy campaign. There should, therefore, be an adequate number of well-equipped dispensaries to carry out the following activities:

(*a*) Health education and propaganda.

(*b*) Protection and control of contracts.

(*c*) Discovery of new cases, with special attention to those of the indeterminate group because of their possible evolution to the lepromatous type.

(*d*) Treatments of patients and contacts according to standards previously stated.

(*e*) Selection of the cases which should be hospitalized.

(*f*) Training of technical personnel.

(*g*) The carrying out of epidemiological investigations.

4. *Preventorium:* This should also be an active organization, the primary aim of which is the removal of children from infectious environment. Its technical activities should be carried out in accord with the following points:

(*a*) Children in contact with lepromatous cases, who are lepromin negative, should be given priority for admission.

(*b*) The interned children should be subject to close observation, especially those which are lepromin negative.

(*c*) Induction of lepromin reactivity by means of B.C.G. should be practiced, and preventive treatment should be given to those who remain lepromin negative.

(*d*) Reintegration into society of the children who have completed their periods of observation, which should be as short as possible. If necessary, observation should be continued by social service organizations.

(*e*) Education of the interned children, which should be carried out preferably by institutions, public or private, located outside the preventorium in order that their future reintegration in society may be facilitated.

5. *Research institution:* Such institutions, adequately supported, should be provided to study the disease with respect to its epidemiology, prevention and treatment.

RECOMMENDATIONS

1. Because of the efficacy of the new medicaments, it is reasonable to assume that these drugs will reduce considerably the period of contagiosity of the lepromatous cases. To investigate this matter, which we regard as of great importance, extensive investigations should be carried out in countries where institutional isolation is impracticable, with the aim of determining if there is any reduction of the incidence of leprosy among the contacts of lepromatous cases.

2. The Committee recommends that B.C.G. vaccination be introduced in the prophylaxis campaigns. It also recommends that adequate studies be carried out, under the most varied conditions, to determine the exact value of this measure and of the induction of lepromin reactivity by B.C.G. It would be of value to compare the possible differences of the protective effect of B.C.G. vaccination among contacts who are removed from infectious environments and among those who are not separated.

3. The Committee recommends that the public health services of the different countries send, periodically, to the World Health Organization information concerning the prevalence of leprosy. The Committee reaffirms that leprosy belongs to the group of infectious and contagious diseases, and that consequently definite measures of control should be employed when dealing with it.

4. The Committee, having in mind the advances made with the new medications, recommends the revision of existing legislation in the different countries. This should comprise the modern basis of control and social assistance, as set forth above.

5. It is recommended that the children of leprosy patients separated immediately after birth should, by preference, be placed with families, or institutions, public or private, which are designed for the protection of infants in general, and not in preventoria for leprosy contacts.

SOCIAL ASPECTS*

PREAMBLE

For many years it has been increasingly recognized that the psychological factors involved in any disease, and especially in a chronic one, are of importance in the treatment of the patient. This is especially true with leprosy, an ailment which for centuries has been feared and abhorred.

This Committee considers it important that the Congress, while recognizing the difficulty of making detailed recommendations because of the widely divergent conditions existing in different countries, shall approve—in general terms—remedies for those factors which plan an important part in the emotional state of the leprous patient. Is it not, after all, prejudice—growing out of ignorance of the true nature of the disease on the part of the patients,

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* The Committee on Social Aspects was composed as follows: Mr. Perry Burgess, *Chairman*, Dr. A. Salazar Leite, *Secretary*, and Drs. Luis Arguello Pitt, Harry L. Arnold, Jr., Felix Contreras, F. Hemerijckx, D. Maldonado Romero, L. Martinez Kleiser, and Etienne Montestruc, *members*.

family, friends and neighbours—which causes him to be feared and shunned, and which thus most deeply disturbs his state of mind? And this same state of mind causes him, far too often, to hide his identity behind a false name, even when his own is an honourable and respected one, and even to fear to present himself for treatment.

REPORT

1. The Committee approves the action at the Havana Congress with regard to the words "leper" and "leprosy." (See Addendum.)

2. The Committee recommends that the Sixth International Congress applaud and encourage efforts now being made for the rehabilitation of the patient with leprosy, and in particular the programme of education for laymen and physicians in regard to the disease.

3. The Committee regards gainful work as of primary importance in the treatment and rehabilitation of patients with leprosy. In each country, choice of occupations must be made according to local circumstances. Governments and private institutions are urged to make every effort to guarantee work to patients discharged from institutions, in compliance with local public health regulations. Vocational training should be provided for those patients needing it.

4. The Committee recommends that there be as little interference as possible with the normal lives and usual occupations of leprosy patients certified by leprologists as non-contagious, in so far as this is consistent with local public health regulations and the patients' own medical well-being.

5. The Committee recommends approval and encouragement of the provisions of governmental assistance for the support of the dependent families of patients isolated, or otherwise disabled because of leprosy.

6. The Committee approves the care of patients with disabilities or permanent deformities in special institutions, so that the atmosphere among patients who are not so disabled or deformed will not have an unfavourable influence.

7. Private institutions for social relief, and those institutions which are collaborating with the governments to prevent, cure or control leprosy, should receive as much assistance from their governments as is consistent with complete freedom of action within the framework of the public health laws of the country.

8. The Committee recommends that existing laws in all

countries be brought up to date and raised to the same level as the modern concepts that are the basis of our present prophylactic campaign.

ADDENDUM

With regard to paragraph 1 of the above report, the decisions of the Havana Congress on the words " leper " and " leprosy " were, briefly:

That the use of the term " leper " be abandoned in favour of " leprosy patient " (or the like); that the use of any such term, in any language, to which unpleasant associations are attached should be discouraged; but that " the term ' leprosy ' should be retained as the scientific designation for the disease."

NOTES ON SOME PAPERS PRESENTED AT THE MADRID CONGRESS

It is impossible to deal satisfactorily with the 200 odd papers presented, for the proceedings of the Congress are not yet published, and the full text of the papers is not available. The abstracts of papers presented at Madrid, were mostly not written in English, two-thirds being either in Spanish or Portuguese. The full papers and abstracts, when they become available, will mostly be in languages other than English. In spite of the difficulties, an attempt to present in broad outline the main points of these papers in the English language appears justified.

Fortunately, Dr. J. Ross Innes has, with what must have been vast labour, translated into English a very large number of the available abstracts and sent them to this office for possible publication. The editor has got a few more translations made of abstracts not included in the manuscript of Dr. Ross Innes. As the result we have available English abstracts of some 200 papers presented at Madrid. (Of a few papers, however, no abstract of any kind is available.)

In the present notes it is proposed to make some general view of this mass of material, and to mention briefly many of the papers. The editor has noticed especially those papers that interested him, sometimes because they reported matters quite new to him, sometimes because they tended to confirm his views, and sometimes because they went quite contrary to his views, sometimes contrary to views generally accepted.

CLASSIFICATION OF LEPROSY. Papers on classification numbered 14. Little discussion of these papers is presented here. Most papers reflect the view that leprosy is of two main more stable types, " tuberculoid " and " lepromatous," but that other less stable and less characteristic forms are seen; and that the classification must be primarily clinical. One paper (Khanolkar and Cochrane) places much emphasis on the lepromin test, and states that " to base classification *solely* on clinical grounds is unscientific " (but no one suggests doing this). Martino Dominguez wants to class " maculo-anaesthetic " cases as almost a third main type. Montel's paper contains some controversial statements; example: the histology of the tuberculoid type is not specific; most cases first present themselves as tuberculoid, and may later become lepromatous; the Mitsuda test is useful, but too variable to provide a criterion for classification.

The view is expressed in several papers that classification must be simple, and should not attempt too much clinical description.

TREATMENT OF LEPROSY. Papers on this subject number 53. Fourteen papers deal with sulphones. It is impossible to notice all of these; many different sulphones are discussed; no outstanding case is made for any one sulphone. Results with all are good, but with the well-known limitations. Laviron *et al* speak highly of the value of intramuscular injections of dapsone suspended in chaulmoogra oil in the large scale treatment of out-patients. They give injections of 1·25 gm. twice monthly, and find that a reasonable blood level is maintained. They think that the amount of oil used is far too small to have any effect, but the oil forms a very good vehicle for slow absorption. They say that 1·25 gm. twice a month is active, non toxic, and practicable for mass treatment.

Herrera records the beneficial effect of sulphone treatment on the menstrual cycle and reproductive systems in female patients. During pregnancy, the puerperium and lactation, improvement under treatment continues. Children born have remained free from leprosy, although remaining with leprous parents.

Five papers deal with thiosemicarbazone, all of them favourably. Laviron *et al* have used weekly intramuscular injections of 600 m.g. in chaulmoogra oil, with benefit.

Nine papers report on isoniazid in human leprosy. All report excellent tolerance and improved sense of well-being, but most record only moderate improvement in the leprosy, and only for a limited period. One report (Laviron and Lauret) deals with isoniazid given alone or in association with other drugs, including DDS, and streptomycin. In neither case could they attribute much

benefit to the isoniazid, though improvement in general condition was recorded.

In murine leprosy, five papers record a marked action of isoniazid in reducing the infection. Two of the five papers record findings indicating the development of drug resistance. Bushby and Barnet record that the beneficial action is only temporary, and that in spite of continued treatment, death from general massive infection occurred at one year. Organisms from these dead animals, when injected into fresh animals, were drug resistant. Drug resistance was demonstrated in animals treated for 6 months. They stated that isoniazid should be used in leprosy only in combination with other known antileprosy drugs.

Tegeler reports that relapse occurred in treated animals when the drug was stopped, and that resumed treatment produced a poor response.

Miscellaneous articles on treatment number 21. A series of articles by Doull, Davison and Guinto reports the methods and findings of the therapeutic trials conducted by the Leonard Wood Memorial. Five treatments were studied, and a control group. Diasone, D.D.S. dihydrostreptomycin, dihydrostreptomycin plus diasone, dihydrostreptomycin plus P.A.S. In general, all the treatment groups showed more improvement than the controls; of the five treatments, none was clearly superior to the others; there is no evidence that a sulphone combined with streptomycin offers any advantage. At one centre, P.A.S. appeared to have some effect.

Wolcott and Ross state " In recent years a number of instances of rapid extension of the leprous processes have occurred in Carville patients while they were receiving continuous sulphone or other treatment." Their paper gives details and photographs of three such cases, one after seven years' treatment, one after ten years, one after six years. (This paper is reprinted in the *International Journal of Leprosy*, Vol. 21, p. 437).

Ramos E. Silva and Peryassu report excellent results from dihydrostreptomycin, later with oral sulphone added, in tuberculoid cases.

Floch regards sulphones (especially D.D.S. and mono-substituted sulphones), thiosemicarbazones, and the isoniazids, as giving uncontrovertible results in leprosy. Sulphones (particularly D.D.S.) constitute the basic treatment; D.D.S. is active and well tolerated when the dose is increased slowly. Treatment is of great value in the non-lepromatous forms of leprosy, and prevents the development of lepromatous leprosy, which fact may be more important than the cure of lepromatous cases. He uses much adjuvant vitamin therapy, Vitamin B complex, Vitamin C & D,

Vitamin K, Vitamin E, Vitamin P.P. for various complications.

He concludes that for many years the leprologist was appalled by the inefficiency of his therapy. Now this is not so. Modern treatment, particularly D.D.S., encourages the idea that the leprosy problem in French Guiana can be dealt with.

Gay Prieto recommends the use of local injections of cortisone in accelerating the resolution of large lepromatous swellings, especially on the face.

Only two papers discuss chaulmoogra oil as a therapeutic agent. Schujman, while not denying the value of sulphones and other agents, protests that chaulmoogra oil should not be abandoned.

The drugs discussed by others include sulphones and thiosemicarbazones and isoniazid, streptomycin, chloramphenicol, P.A.S., A.C.T.H. and cortisone, aureomycin, succinic acid, and an antigen prepared from a culture obtained from leprous tissue. No point of major interest is brought out in these papers.

One paper, by F. Contreras *et al*, records good results in cases of lepra reaction from the intravenous transfusion of heterogenous plasma, or whole blood.

One paper by Scippa and Cotlear (of Peru) reports good results in reactional leprous neuritis by the use of the spinal pumping method of Speransky (removing by lumbar puncture a " certain amount " of cerebro-spinal fluid, and the immediate return of the removed fluid, this procedure being repeated up to 20 times).

Gaté and Rousset write of experiments in treatment of leprosy with the antigen of Marie Suzanne, Sohier and Noel (see under bacteriology). Good results are reported in all forms of leprosy, but the complications include local reactions, general reactions, skin eruptions, neuritis, temporary aggravation of iritis etc. In the tuberculoid type of leprosy, the nerve lesions are said to improve rapidly.

Amendola discusses eye, ear, nose and throat complications in leprosy, and describes how surgical and medical measures and sulphone treatment have greatly improved the outlook.

Farina discusses surgical measures to graft eyebrows and repair deformed noses.

THE LEPROMIN TEST. Twelve papers relate to this test and its mechanism and significance. Bechelli *et al* correlate clinical findings in the patient with the histopathology of the skin at the site of the test and find that weakly positive Mitsuda reactions are often significant.

Wade injected cortisone into dogs, generally, and locally, and

studied the modification of the Mitsuda test produced by this hormone. He found that during the time of its action, the hormone prevented the skin reacting to lepromin, but, when the action of the hormone passed off, the reactions developed normally. In man the same thing was found. Fernandez, making similar studies in man, injected hydrocortisone locally into the skin, immediately following it with an injection of lepromin. The early (Fernandez) reaction was largely inhibited, and also the late Mitsuda reaction. These results appear to be quite different from those of Wade.

Zubiri studied, (as also did Wade) the effect of adding hyaluronidaze to lepromin just before injection. The results are difficult to understand in the only available abstract, but apparently the lepromin diffuses widely and reduces the local reaction. Neto and Diniz report that dilution of the standard lepromin produced little reduction in the reactions. Dauden Sala reported that a repeated Mitsuda test frequently induced a swelling at the site of previous tests. He found this commonest in definite " contacts," and that this reactivation is a good prognostic sign.

Dharmendra studied early and late reactions produced with lepromin prepared (a) by long chloroform extraction and grinding of the tissue, (b) by Wade's method, using no chloroform, and (c) short chloroform extraction and grinding. He found that (a) gave more early reaction and less late, (b) gave more late reaction and less early, and (c) gave reactions between (a) and (b).

Fernandez studied the mechanism of the lepromin test, detecting two factors, specific (due to *M. lepræ*) and non-specific (due to *M. tuberculosis*). Tuberculin-negative children who have been exposed to leprous infection are often Mitsuda positive, and tuberculin- and lepromin-negative children can sometimes be made Mitsuda positive by the injection of lepromin. The effects of repeated injections of lepromin depend on the nature of the antigen used; the bacillary antigen can increase reactivity, and the protein antigen can reduce it, with diminution of the early reaction but persistence of the late one.

A study of the lepromin test was made in tuberculous children, and tuberculous infection was indicated as the cause of the positive Mitsuda test. The injection of an oily suspension of Koch's bacillus killed by heat could produce a lepromin conversion.

B.C.G. in healthy persons produced lepromin conversions in 90% of cases. The early (Fernandez) reaction is thought to indicate hypersensitivity, and the late (Mitsuda) reaction a state of resistance to *M. lepræ*.

Fiorello and Bechelli studied the lepromin test in relation to

plasma protein changes in leprosy and other diseases. In lepromatous leprosy the plasma protein changes are accompanied by a negative lepromin test, but in other diseases associated with similar plasma changes (lymphosarcoma, Hodgkins disease, chronic myelosis, visceral leishmaniasis etc.) the lepromin test was usually positive.

Gaté and Roussel studied the influence of injections of the antigen of the Marie Suzanne, Sohier and Noel on the immunological reactions in leprosy and in tuberculosis. Intradermal injections of this antigen produced no reaction in healthy people; in ten cases of dermatosis the only reaction was in one case of skin tuberculosis in which there was slight late local reaction, but there was reactivation of the von Pirquet and improvement in the lesions. In cases of leprosy (of all types) there was immediate local reaction, all intense, often focal reaction in the lesions, sometimes general reaction. The influence on the lepromin test was (a) if given at the same time as the lepromin, the Fernandez phenomenon, (b) if given after the lepromin, a reactivation of the previous Mitsuda phenomenon, (c) if given before the lepromin, an increase in the positivity.

B.C.G. Fernandez reported over 90% lepromin conversions produced by B.C.G. Souza *et al* reported on a study of the influence of B.C.G., living or dead, on the Mitsuda reaction. Children were given (orally) 600 mg. of B.C.G. living or dead. Conversions were produced by both. Some conversions were seen long after the B.C.G. was given. They noted an absence of relation between the Mitsuda and tuberculin reactions.

De Souza Campos reported favourable early results of B.C.G. vaccination in reducing the incidence and severity of leprosy. (See *Int. Jl. of Lep.* **21**, p. 307).

Bechelli and Quagliato studied the incidence and form of leprosy in contacts who had been treated with B.C.G. One thousand six hundred and fifty-eight contacts were studied for one year. Twelve became definite cases of leprosy, mostly tuberculoid. B.C.G. appeared to reduce the tendency to develop lepromatous leprosy. The authors state that the absence of adequate controls prevents further conclusions.

Convit *et al* report studies of 107 persons originally lepromin-negative and with no clinical evidence of leprosy, in contact with lepromatous cases of leprosy. B.C.G. was given by injection in July, 1950 to 106 of the 107; 95% showed lepromin conversions. The negatives were revaccinated later. In March, 1953, all the 107 were examined and lepromin tested. Three had " incipient " lesions, histologically tuberculoid; all three had strongly-positive

lepromin reactions. The single one of the 107 who had not been vaccinated had developed lepromatous leprosy.

Floch records that the adult is susceptible to primary leprous infection; European adults arriving in French Guiana not infrequently develop the disease. After 100 years of the penal settlement, there is more leprosy among the penal element of the population than among the free Creole population. B.C.G. may modify beneficially the reaction of persons tissues to leprous infection, and its use should be encouraged. Souza *et al* studied lepromin conversions in children (a) given B.C.G. and (b) not given B.C.G. Within one year the spontaneous conversions were considerable in number, but the B.C.G. group showed a higher conversion rate.

Rotberg discusses the immunology of leprosy, repeating his old theory that an inherent constitutional factor (N) influences the ability of the individual's tissues to respond by lepromin positivity to tuberculous infection, to B.C.G. vaccinations, or to other similar but unknown factors. The minority have no N factor, and the value of B.C.G. in this minority is very doubtful.

Schujman reports that in lepromatous cases, Mitsuda negative, in a considerable number the Mitsuda test can be made positive by giving intradermal injections of antigen made from the Stefansky bacillus (rat leprosy), or by giving B.C.G. by mouth. The early (Fernandez) reaction does not become positive; moreover, the Mitsuda conversions are often temporary. The results with the Stefansky bacillus are considered important, as showing that other acid-fast bacilli besides the Koch bacillus are capable of provoking the co-sensitization phenomenon in leprosy. Several papers discuss these temporary lepromin conversions in lepromatous cases produced by B.C.G.

Azulay *et al* gave 57 rats B.C.G. (20 mg. inoculated), and 115 days later infected them with Stefansky's bacillus, 20 other rats being used as controls. The rats inoculated with B.C.G. showed smaller lesions, and less dissemination. The B.C.G. seemed to have some protective value.

Azulay *et al* produced lepromin conversions in guinea pigs by injection of B.C.G.

Several papers discuss lepromin conversions seen in children after living B.C.G., sometimes dead B.C.G., and sometimes spontaneously.

GENERAL IMMUNOLOGY. There were eight papers on other aspects of immunology. Hale and Molesworth, from studies, in Malaya, of lepromin and tuberculin tests in healthy people, persons with leprosy, and persons with tuberculosis, suggest that it is not the

response of a person's tissues to the leprosy bacillus which determines the type of leprosy, but the opposite, the type of the disease which determines the response (allergic or otherwise) to the leprosy bacillus. They feel therefore that B.C.G. vaccination in Malaya will have little effect in prophylaxis.

Gay Prieto and Contreras discuss immunity and susceptibility to leprosy at different ages. They discuss the relative susceptibility of young children and the relative immunity of adults. They give details of one unsuccessful attempt to infect an adult by many injections. They quote however six cases in which natural infections occurred in adult life. They conclude that no age is free from danger of leprous infection.

Blanc reports experimental work with the "Chauviré" antigen (furnished by the Society for the Propagation of the Faith, at Lyons, and derived from a culture of acid-fast bacilli from human leproma). One thousand three hundred and nineteen leprosy patients or contacts have received injections of this antigen. The present report deals with the first 400. The numbers in each group are not given in the available abstract. Mitsuda negative non-leprous persons all became Mitsuda positive. Mitsuda negative persons with leprosy showed a larger proportion of conversions, 100% in tuberculoid cases, 50% in lepromatous cases and 68% in indeterminate cases. Mitsuda positive healthy persons remained positive. Mitsuda positive cases of leprosy sometimes became negative; 36% of indeterminate cases, 20% of lepromatous cases, and 6·5% of tuberculoid cases.

Bechelli *et al* report on the use of the eosinophil test of Thorn and R.P.K. to explore suprarenal function in leprosy in relation to the lepromin test. There was no close correlation between the activity of the suprarenals as revealed by these tests and positivity in the lepromin test.

de Mesquita considers that immunological phenomena in leprosy (presumably the lepromin test with lepra bacilli) are variable because the leprosy bacillus is not the cause of leprosy; the presence of this bacillus is only a useful index of the existence of the symptom-complex which seems to make up leprosy. The arguments he uses to support this view cannot be summarised here.

CLINICAL STUDIES. Papers on this subject number 11. Molesworth and Hale report on the peculiar features of leprosy as seen in Chinese and Malays, the chief feature being the frequent development from tuberculoid to lepromatous leprosy through an atypical intermediate phase, with correspondingly varying lepromin tests and histopathology.

Gay Prieto describes two cases of spontaneous cure of lepromatous leprosy, the cures now being of long standing.

Dauden Valls and Dauden Sala discuss the clinical features and classification of skin lesions in 90 children in a preventorium.

Garcia Perez *et al* discuss the " leprosy of Lucio " which they consider to be an infrequent form of " reaction " in lepromatous cases producing ulceration.

Nunez Magro *et al* discuss the surgery of tendons in leprosy.

Dubois and Radermecker discuss the value of neuro-muscular chronaxy in the study of leprosy. In neuritis and toxic changes in nerves and muscles, chronaxy increases, sometimes markedly. The determination of chronaxy is found to be useful, sometimes in diagnosis, in prognosis, and in studying the effect of treatment.

Miranda and Tramujar describe a case showing nothing but a lepromatous neuritis of one ulnar nerve.

Garcia Perez *et al* describe clinical varieties of the lepromatous type of leprosy.

Hayashi presents a clinical and histopathological study of erythema nodosum leprosum.

Lavalle Aguilar P. *et al* report a case of a hand infected with *M. ulcerans*, with necrosis. It responded to treatment with D.D.S.

PATHOLOGY. Papers on this subject number 18. Sagher writes on the " isopathic phenomenon." In lepromatous patients, injections of the following substances were made into the skin, and skin was later taken by biopsy for histological examination: tuberculin, leishmanin, milk, peptone, B.C.G., living *Leishmania tropica.* He concludes that lepromatous leprosy produces only its own histopathological response (namely lepromatous infiltration), irrespective of the cause of the lesion. This phenomenon he calls the isopathic phenomenon. He thinks it may be useful in diagnosis.

Wade discusses the histopathology of erythema nodosum leprosum. It is not at all distinctive histologically; its nature and causation remain unexplained; it is undoubtedly an allergic phenomenon.

Portugal, studying the same subject, reports on collagen changes in the tissues, commenting on previous reports of others, and presenting his own findings.

Chover Mandramany discusses the pathology of perforation of the nasal septum in leprosy, which is caused by lepromatous infiltration followed by complete absorption of the cartilage.

Aguirre *et al*, and Llombart and Alcacer describe the lesions of the liver in leprosy, and the latter paper describes siderosis (deposit of iron) as common, and cirrhosis as sometimes seen.

Mut Mut describes bone lesions in leprosy as being specific or non-specific. Specific changes are produced in the bone marrow, and in the bone itself, by lepromatous infiltration; it is most marked in the shaft of bones. Bone destruction is followed by very little regeneration. Non-specific lesions are due to neuro-trophic changes and secondary infection. Neurotrophic changes produce rarefaction and absorption, and secondary infection, periostitis, and sometimes osteomyelitis.

Alvaro Lopez *et al* write of radiography of the long bones in leprosy.

A series of four papers, two by Moller Christenson, one by Melsom and one by Waaler, deal with a curious and interesting subject. A farm in Denmark was on the site of a mediæval leper home, with church and burial ground used from about 1250-1550 A.D. The burial ground was excavated and revealed 50 intact graves, and 150 extra skulls, and an estimate was made of the total number of graves as over 1,000. Of the skeletons or part skeletons, 107 were males, 77 females, 6 uncertain and 7 children; average age was 33 years. In 80% of the skeletons in which the hands and feet revealed definite leprous change, the maxilla showed characteristic changes also, atrophy of the alveolar process and of the anterior nasal spine. These changes were found in 110 of the 150 skulls. Moller Christensen calls this " facies leprosa." Moller made similar findings in a Norwegian leper graveyard. Patients with leprosy were x-rayed and showed the same bone changes. Waaler made similar findings of bony changes in autopsy material of cases of leprosy. He attributes it to bone resorption caused by chronic inflammation of the overlying soft tissue.

Wilkinson and Cardama studied the presence of lepra bacilli on the horny epidermis covering lepromatous lesions. They collected the scales from not more than 1 sq. centimetre of unbroken skin. Of 50 examinations, 12 cases, all lepromatous, showed bacilli. In no cases were they abundant, but they consider this discharge of bacilli from unbroken skin to be important.

Hayashi studied the phagocytosis of leprosy bacilli and other acid-fast bacilli by the leucocytes of leprosy patients, by special methods. The leucocytes from lepromatous cases were most phagocytic, from " neural " cases least, and from tuberculoid and indeterminate cases intermediate. In normal persons phagocytosis was little.

Hayashi also presents a study of bone lesions in leprosy based on radiographical, histopathological and anatomical studies.

BIOCHEMISTRY AND SEROLOGY. Miguel *et al* present a study of

plasma proteins in leprosy by electro-phoretic methods. The findings were as have previously been reported by others, a gamma globulin increase with albumen globulin ratio inverted. Other tests were used for comparative purposes, namely the blood sedimentation rate, Cadmio test, Takata Ara reaction, and the Weltmann band.

Arjona *et al* present a study of plasma proteins in the different clinical forms of leprosy, and Mauzé and Arnaud on electrophoresis of serum in leprosy.

Gonzales Medina and Alfonso Gordon studied the urinary secretion of 17-ketosteroids in lepromatous leprosy. Low figures were found in all cases, indicating profound endocrine derangement.

Floch *et al* studied in leprosy some classical serological tests for syphilis and the spirochaete immobilization test of Nelson Mayer. Of 77 sera studied, 37 gave positive results in one or more of the classical tests, but only 11 of the 37 gave positive Nelson Mayer tests. These eleven sera however gave strong positive results in the classical tests, while the other 26 gave only weak positive results. Thirty of the 40 sera giving negative results in the classical tests were Nelson Mayer tested and one positive was recorded.

These results show that in leprosy with strongly positive classical tests, particularly if several different tests are positive, one must not ignore the possibility of syphilis.

Gaté *et al*, and Vilanova and Catasus write of the Nelson Mayer test in the presence of leprosy as being specific for syphilis.

Montestruc *et al* give two papers on the Middlebrook-Dubos reaction of hæmagglutination with an antigen prepared from tuberculin. They find the test to be positive in high titre in severe untreated lepromatous cases, and the titre to fall as the disease subsides under treatment. In non-lepromatous cases the same is true, but at a lower level. The test may be of value in classification and in assessing progress.

Rodrigo Abad and Lopez Contreras write of the Gaté and Papacostas reaction as a test for plasma protein changes in leprosy, and Rodrigo Abad *et al* of the coagulation band of Weltmann in studying the same matter.

BACTERIOLOGY. There were six papers (of three no abstract is available).

Gray and Hanks studied respiration and hydrogen transfer capacity of human and murine leprosy bacilli, and showed persistent endogenous metabolism; anærobiasis reduces respiration and infectivity. Leprosy bacilli differ from cultivable pathogens (a) by inability to acquire energy *in vitro* and (b) by extreme susceptibility

to the inhibitory action of lipo- and muco-proteins in serum and body fluids. Infectiousness depends on metabolic capacity. Apart from immunological mechanisms, two types of antibacterial action appear capable of reducing pathogenicity: (a) anærobiasis and extracellular inhibitors, (b) the reduction by chemotherapeutic agents of access to energy.

Sulphones are fatal to cell cultures; they may modify cells so as to expose bacilli to extracellular inhibitors. Streptomycin is confined to extracellular fluids. Isoniazid inhibits intracellular mycobacteria. Its action depends in part on combination with heme-type compounds in the respiratory system of mycobacteria. It is the most effective drug known in murine leprosy.

Alexander-Jackson reports on a pleomorphic organism consistently isolated and grown, in transferable cultures, from the blood of leprosy patients. Improved media have given more vigorous growth, and vaccines, skin testing, and serological testing agents can be prepared. Reports of such tests are not available.

Marie Suzanne, Noel and Sohier write of anatomo-pathological studies of lesions produced by "*Mycobacterium marianum*" isolated from leprous lesions. (No abstract is available.)

Rivas presents three papers on studies of mycobacteria found in the ranchos from which come most of the leprosy cases of Colombia. He studies such organisms in the insects found in the ranchos, and in sweepings from a leprosarium. He summarises his 1,669 attempts at culture of acid-alcohol fast bacilli from leprous material, and from other (natural) sources. He finds such bacilli very common, in nature, and speaks of the need for classification of these innumerable acid-alcohol-fast bacilli.

Gonzales Prendes *et al* write of fluorescent microscopy of the leprosy bacillus, giving details of technique and enumerating its advantages, which they consider great.

EPIDEMIOLOGY AND CONTROL. Thirty-five papers on this subject were presented. Only a few can be mentioned here.

Littann, in two papers, discusses leprosy in Europe, including what is known of its introduction in each country, the developments through the centuries, and the position in 1950. The figure 20-23,000 cases is given for cases of leprosy in Europe in 1950.

Davey describes the large leprosy problem in Nigeria and the organisation of anti-leprosy work.

Blanc writes that in French Cameroons classical isolation has been abandoned as inefficient and impracticable. It has been judged more effective to reorganize the campaign so as to sterilize

the reservoir of the infection by treatment, and to immunize contacts.

Martinez Dominguez writes of the profound influence of sulphone treatment on control of leprosy in Spanish Guinea. He records a great increase in the number of cases recorded (many new patients being attracted by treatment), and a marked fall in the death rate of the patients. He thinks that the voluntary reporting of early cases, the great increase in early diagnosis, the improved results of treatment with reduced infectivity, making possible more out-patient treatment, the marked change in the attitude of the patients, fearful suspicion engendering rebellion, protest and non-co-operation being replaced by willing co-operation and great interest in treatment.

Laviron and Lauret write of the Mobile General Hygiene and Control Service and its work for leprosy in French West Africa, in an area with a population of 16 millions. From 1946 to 1952 three million people have been examined each year for leprosy, and over 120,000 cases recorded. Four hundred and four treatment centres function; 53,000 patients were treated in 1952. The introduction of " deposit therapy " by injection of D.D.S. in oil once a fortnight has recently allowed a great extension of sulphone treatment. The service, by its persistence, by the growing reputation of the treatment centres, the results obtained over several years, is commanding the trust of the people, and it will play a big part in the success of the leprosy campaign.

Guinto describes the field studies carried on for 15 years in Cordova and Talisay by the Leonard Wood Memorial and the Philippine Government, with observation of the entire population. The report records marked changes in the prevalence of lepromatous and non-lepromatous leprosy; the incidence of leprosy according to degree of exposure to various forms of leprosy; lepromin reactions of 2,000 persons; statistical studies of mortality of leprous cases, and the risk of conjugal exposure. The abstract gives no details on these points.

Buker describes the development of anti-leprosy work where medical and financial resources are meagre, with main stress on the training of lay personnel in the diagnosis and treatment of leprosy, on the establishment of treatment centres, with, later, when time and funds permit, surveys. Laboratory work, detailed examination and records, and " elaborate colonies " can await adequate funds.

Many papers on epidemiology and control deal with limited areas and are mainly of local interest.

Most papers on control reflect the limitations of isolation measures, and lay stress on early diagnosis, chemotherapy, and

sometimes immunization of contacts. These measures are confidently expected to produce results. The changed outlook produced by modern treatment is repeatedly stressed.

SOCIAL ASPECTS. On this subject there are six papers. None calls for special mention. The need for surgical measures to aid in rehabilitation, for occupational training, for the procurement of occupation, and for financial support till rehabilitation is complete, is stated.

Weaver, discussing " Preventoria " for children, states that in Brazil of 5,000 children of leprous parents cared for, only 206 have developed leprosy.

HISTORICAL. Papers number three.

Wolker discusses the old question of leprosy in pre-columbian America, and in another paper studies the records of experimental and accidental transmission of leprosy; cases of accidental transmission are much more numerous.

REVIEWS

International Journal of Leprosy, Vol. 21, No. 3 (July-Sept. 1953).

Leprosy in Children in French West Africa, by Laviron and Lauret.

The problem of leprosy is a serious one in French West Africa and the disease seems to be on the increase. The total number of children with leprosy is estimated as 30,000. Familial infection is the rule, and it appears that not only are lepromatous cases responsible for the spread, but also tuberculoid and indeterminate cases as well. The majority of cases start between the ages of 5-15. The onset is usually indeterminate, and later one of the polar forms develops. Only 10-15% are lepromatous. Treatment with sulphones combined with chaulmoogra oil is confined to the lepromatous cases. The only practical form of prophylaxis possible is medical inspection of schools with the segregation and treatment of all children with leprosy.

B.C.G. in the Prophylaxis of Leprosy. A preliminary report, by Nelson de Souza Campos.

The writer is convinced that a BCG induced positive lepromin reaction has the same significance as the natural reaction, and that persons who have had no contact with leprosy and show a positive lepromin reaction undoubtedly have had a primary infection with tuberculosis. There may, however, be congenital conditions, intrinsic or constitutional, which render a person positive or permanently negative to lepromin.

In Sao Paolo from Feb.-Dec. 1952, 1,658 contacts were given 3 weekly doses of 200 mgm BCG by mouth while 3,329 contacts had no BCG. Up to Jan. 1953 10 cases of leprosy, all tuberculoid, had appeared amongst the vaccinated (0.6%), whereas amongst the unvaccinated 179 (5.4%) cases of leprosy had occurred—47 lepromatous, 84 undifferentiated, and 48 tuberculoid.

As this is only a preliminary report; the writer agrees that later reports may alter the picture.

The value of the Lepromin reaction in the diagnosis of clinical forms of leprosy, by Salomon Schujman.

The writer holds that whereas the classification of a case of leprosy should be based on combined clinical, bacteriological, histopathological and immunological criteria, yet the last is the most important as the lepromin reaction is the most stable. Other factors change with the progress of the disease but the lepromin, especially the late Mitsuda phenomenon, remains practically fixed throughout. It is of the greatest value in indeterminate cases, where a negative lepromin nearly always indicates that the case will become lepromatous.

Study of the morphological modifications of Mycobacterium leprae during chemotherapy, by M. G. Malfatti and E. D. L. Jonquieres.

Using the electron microscope with direct and shadow casting technique, the writers noted changes in the M.leprae after treatment with sulphones, isoniazid and thiacetazone. They found that swelling of the cytoplasm and the granular state are signs of the first modification of morphology, and also the disappearance of the peripheral halo which is apparently dependent upon the normal bacillary metabolism. They believe that modern chemotherapy holds out great hope in the eradication of leprosy.

Staining of M. leprae by the Rio Hortega Silver method in frozen and paraffin sections, by Jose Sanchez.

Rio Hortega's method of double impregmentation with silver without reduction is described in detail. Owing to the argentaffinia

of leprosy bacilli, the writer claims that many more bacilli are seen after such staining than by the regular Z.N. or Gram Weigert techniques.

A Review of recent animal inoculation studies with human and murine leprosy bacilli, by T. Tanimura and S. Nishimura.

Ten years of experimentation failed to produce any infection in fowls or other animals with human leprosy bacilli. Repeated attempts to infect fowls with murine bacilli also failed. The human bacillus finds only the human being a favourable host, and the murine bacillus is limited to rats, mice and hamsters. The ocular tissue which has an affinity for many pathogenic organisms could not be made to react differently to the race specificity. All attempts to alter the constitution of animals failed to induce infection with leprosy.

G. O. TEICHMANN.

Modern Concepts of Leprosy by Harry L. Arnold, Jr.

This small book is by a dermatologist with a wide experience of leprosy. Written primarily for doctors who are not familiar with the disease, it will nevertheless prove useful to workers in leprosy institutions. Because of its primary purpose, the greater part of the book is devoted to diagnosis and pathology, and only two very short chapters to treatment and prevention. He urges the great importance of certainty in diagnosis owing to the serious social implications involved, and lays down the minimal diagnostic criteria required:—(1) Either the presence of acid-fast bacilli morphologically consistent with M. leprae obtained by Wade's scraped incision method from lesions, and not obtained only from nasal scrapings, ulcers, or skin surfaces where other acid-fast bacilli are commonly found; or (2) evidence of nerve damage which cannot be attributed to trauma or non-leprous peripheral neuritis. He stresses that in early cases as a rule only one of these criteria, not both, can be satisfied. It is often taught that leprosy attacks either the skin or the nerves, but in both types both are affected in almost all cases.

With regard to epidemiology, very few positive statements can be made, as it is full of curious contradictions and paradoxes. It is generally accepted that leprosy is only mildly contagious and is usually contracted in childhood after prolonged contact with lepromatous cases. However, many cases can remember no known contact with the disease, and numerous instances have occurred in individuals clearly exposed for the first time in adult life. Also, attempts to transmit leprosy by inoculating human volunteers with

fresh presumably infective material have almost uniformly failed. Perhaps the open case of leprosy does not play as vital a role as has been supposed, and casual contact may occasionally suffice to cause infection.

His statement that nodular leprosy is the commonest variety is not the experience of workers in India or Africa where the tuberculoid type greatly predominates.

Dealing with pathology, he says that one can best understand the lepromatous type if one recalls that they are not true inflammatory but rather foreign-body granulomas, in which the M. leprae grow and multiply. They represent a passive phagocytic process rather than an active defensive one. In distribution and configuration they clinically resemble lymphoblastomas, as both are composed of reticuloendothelial cells, and they tend to develop in cool areas of the body. For this reason lesions are usually found on the face, ears, outer limb surfaces, and internally in the nose, larynx and testicles.

The histological changes in tuberculoid leprosy are very similar to those in Boeck's sarcoid. Diagnosis should depend not on biopsy but on nerve damage, the lepromin test and the absence of hyperglobinaemia. The last present in sarcoid and the first absent.

He stresses the importance of the positive lepromin test in differentiating tuberculoid cases. Negative reactions should relegate a case to either the intermediate, borderline or lepromatous type.

G. O. TEICHMANN.

International Journal of Leprosy, Vol. 21, No. 4 (Oct.-Dec. 1953).

Original Articles:

Laviron, P. Lauret, L. et Jardin, C. Contribution a l'eture de la chemiotherapie-retard dans la lutte antilepreuse en Afrique Occidentale Francaise.

Wolcott, R. R. and Ross, Sr. Hilary. Exacerbation of leprosy during present day treatment.

Contreras, F., Guillen, J., Ponziani, J. and Terencio, J. Hemoterapia en las leprorreacciones.

Vilanova, X. and Catasus, J. M. La prueba da Nelson-Mayer (Inmovilizacion Treponemica) aplicada al suero do los enfermos de lepra. (Nota previa).

Sagher, F., Liban, E., Zuckerman, A. and Kocsard, E. Specific tissue alteration in leprous skin. V. Preliminary note on specific reactions following the inoculation of living microorganisms (" isopathic phenomenon ").

Traversa, E. L'etat actuel de lutte contre la lepre en Italie.

Bushby, S. R. M. and Barnett, M. Isonazid resistance in murine leprosy.

Lavale Aguilar, P., Iturribarria, F. M. y Middlebrook, G. Un caso de infeccion humana por Mycobacterium ulcerans en al hemisferio occidental. Nota previa.

Editorials: Wade, H. W. Report on the Madrid Congress.
News and Notes.
Current Literature.

This is the Madrid Congress number of the Journal. The original articles here printed were all presented at the Madrid Congress; the Editorial consists of the Editor's report on the Congress; the Leprosy News and Notes Section runs to twenty-three pages devoted entirely to an account of the Congress, a list of those attending, and its proceedings, the reports of the various technical committees, and to the minutes of the General Meeting of the International Leprosy Association held in Madrid; the Current Literature section gives the titles, and usually an abstract, of all the papers officially presented at the Madrid Congress; they number 166.

Laviron, Lauret and Jardin's article is summarised as follows:—

In French West Africa, where each medical officer has to cover a very large area, the number of leprosy cases that can be treated is the greater the less frequent the treatments, and efforts have been made to develop a satisfactory deposit (retard) method that calls for injections only once in two weeks. It is shown that when DDS in fine crystalline form is suspended in peanut oil—the dose 1.25 gm in 5 cc.—there is rapid absorption, with correspondingly high blood and urine levels for a few days and only traces in the latter part of the period. When chaulmoogra preparations are used, however, there is a more satisfactory deposit effect, with slower absorption of the drug and prolonged maintenance of a useful blood level. The ethyl esters (with 4% guicol) are rather painful, while chaulmoogra oil itself is too viscid for convenience, so in practice a mixture of equal parts of the two is used. The results obtained have been more satisfactory than with other methods of administering DDS. Too little chaulmoogra is used to regard the treatment as one of therapeutic 'association' or 'synergy,' but it is nevertheless regarded as rational to use it rather than an inert vehicle. It would be possible to combine the deposit sulfone therapy with chaulmoogra treatment. 'thus realizing an effective association of medicaments.' ''

Walcott and Ross's article is summarised as follows:—

'' Since 1948 exacerbations of leprosy have been observed in hospitalized patients receiving sulfone and other present-day treatments. Case histories and clinical photographs illustrate typical cases of aggravation of lepromatous leprosy. The cause of the exacerbation is not apparent. Erythema nodosum is usually absent before exacerbation. The possibility of clinical and bacteriologic exacerbation must be considered in evaluating the prognosis of patients undergoing present day treatment.''

The article by Contreras, Guillen, Ponziani and Terencio is summarised as follows:—

'' The authors relate their experience with transfusions of various blood products in the treatment of lepra reaction and certain other conditions, beginning with heterologous plasma (a proprietary calf-plasma

product which gave good results although with frequent untoward reactions), homologous plasma (lyophilized, used on a small scale with no intolerance), autohemotherapy (of limited usefulness), and finally whole blood obtained mostly from blood banks. On the basis of over 400 whole-blood transfusions the results in the various conditions treated are stated in percentages. For example, in severe general lepra reaction some 83% of the cases were cured within three days, and many of them in from 12 to 48 hours. All cases of the erysipelatoid form of reaction cleared up rapidly. On the other hand, in reactions of long duration and moderate severity there was only transitory improvement in 90%. Summaries of several of the more striking cases are given. There were only slight post-transfusion reactions in 20% of the cases, and no severe ones. The procedure is regarded as of great value."

The article by Vilanova and Catasus is summarised as follows:—

"Previous reports of results of the treponema immobilization test on sera from leprosy patients are reviewed, and it is pointed out that they do not permit any conclusion as to whether positive results are obtained more frequently in lepromatous than in tuberculoid cases, the former of which give more nonspecific reactions than the latter with the ordinary tests for syphilis.

Eighteen cases were submitted to various serological tests and the treponema immobilization test, 8 of them lepromatous, 9 tuberculoid, and 1 indeterminate. The data are given in the table (somewhat condensed to conserve space). They had all received considerable treatment, and even those still classed as active were definitely improved. That fact is held to explain why the ordinary serum tests gave positive results in only two cases. In one of them the T.P.I. was definitely positive, while in the other the result was uncertain although the patient was a gypsy who might well have once had syphilis. The results are held to be in favour of the specificity of the test. The study is to be continued."

Sagher, Liban, Zuckerman and Kocsard in previous papers had recorded that in leprous (lepromatous?) patients, the injection of tuberculin, leishmanin, milk and peptone elicited a histological reaction characteristic of lepromatous leprosy, while in normal persons the histological reaction was non-specific. In the present paper the reaction of leprous skin to living organisms was studied, B.C.G. living vaccine and Leishmania tropica cultures being used. In practically all those injected with B.C.G., and in most of those injected with Leishmania, the histological reaction was "lepromatous or prelepromatous." This phenomenon is called the "isopathic phenomenon." Further studies are being made of its possible usefulness "in detecting leprosy in contacts and in determining the effectiveness of chemotherapy."

The article of Traversa is summarised as follows:—

"There were 391 known leprosy cases in Italy at the end of 1952, of which 190 were hospitalized as contagious. The disease exists in coastal regions where there is much maritime traffic and movements of migration. Special attention is given returning emigrants, for early diagnosis. No secondary case has been found in the families of cases discovered early, but there are some in families of such people who had not been diagnosed until late."

"For isolation, there are four special pavilions, connected with dermatological clinics in Bari, Genes, Messina and Cagliari, three of them being enlarged and improved. There is also being built at Pouilles an agricultural colony, on an area of 43 hectares located quite distant from centres of habitation, with a section composed of cottages in which mem-

bers of the same family may live together. Here there may be effected voluntary isolation of patients who are bacteriologically negative and classified as noncontagious.

"It is planned to provide financial aid for both the patients and their families during the period of hospitalization. This measure is expected to aid in the discovery of cases which now avoid detection because of the fear of economic dislocation."

The article of Bushby and Barnett follows on their previous report that isoniazid has a marked effect in suppressing murine leprous infections. They now find that in mice the suppressive action of INH is only temporary, and that this is due to the development of resistant organisms. The resistance was shown by the fact that isoniazid failed to protect further mice infected with spleen emulsions from the original treated animals. It is considered possible that in human leprosy a similar resistance develops, and that this may explain the poor late results of treatment. A plea is made for the trial of isoniazid in conjunction with known anti-leprosy drugs, and not alone.

The article of Aguilar, Iturribaria and Middlebrook describes a case of infection of a finger with *M. ulcerans* with necrosis. Histopathological examination revealed nothing specific. An acid-fast bacillus corresponding on culture to M. ulcerans was isolated. The condition had progressed for two years in spite of treatment. Treatment with DDS, 100 mg. a day for 15 days, and then 200 mg. a day for 8 months. Improvement was slow and steady. Terramycin was necessary to control secondary infection. At the end of eight months, activity of the lesion had almost gone.

The **Reports** of the Technical Committees, as adopted by the plenary session of the Madrid Congress, are reproduced elsewhere in this issue.

Modern Trends in Dermatology (Series 2) Chap. 9 "A Critical appraisal of Modern Trends in Leprosy with particular reference to advances in Immunology, Histopathology and Treatment." By R. G. Cochrane.

This critical appraisal contains some assertions that have not gained universal acceptance at present. The author accepts the results of Khanolkar's work in Bombay in which 20% of healthy contacts of leprosy patients were found to harbour *M. lepræ* in the skin, and states that his concentration method of demonstrating bacilli in so-called closed cases of leprosy has opened up the whole question of the infectivity of these cases, but he considers this should not affect the well-established methods of public health control, as the likelihood of infection is very slight. However, the statement that a positive lepromin reaction indicates that the person is probably harbouring *M. lepræ*, dead or alive, within the tissues is difficult to reconcile with the fact that many people living

in countries where leprosy is absent give a positive reaction. He believes that all persons who come into contact with leprosy and everyone who is infected at first develop a positive lepromin reaction which corresponds with Khanolkar's " Silent phase." From this one of three developments can take place—(1) the tissues may become hypersensitized and give a strongly positive reaction; (2) they may become desensitized and give a negative reaction, or (3) they may remain in an unstable condition—not fully sensitized or desensitized. In Khanolkar's cases, however, all those healthy contacts that give a positive lepromin reaction and later developed leprosy developed, as one might expect, the tuberculoid type.

These three developments lead to the three primary groups or types of leprosy—(1) Tuberculoid (lepride), (2) lepromatous and (3) Dimorphous (Borderline). Taking the lepromin test as guide to grouping, the author considers the disease, according to its clinical manifestations, as Macular, Infiltrative and Polyneuritic. Macules giving a strongly positive lepromin reaction may be simple inflammatory or definitely tuberculoid; those with a negative reaction form the typical uncharacteristic or indeterminate macules of the S. American classification, or form the prelepromatous or lepromatous macules. In sections the bacilli show a " fish swimming up-stream " appearance; and those giving a weak positive are not easy to describe and form the dimorphous group. Infiltrations are similarly divided into (1) Minor and major tuberculoid; (2) lepromatous and (3) Atypical tuberculoid and atypical lepromas. Histological characteristics of the three groups are shown in tabular form.

Polyneuritic lesions. These are not the lesions found in normal lepromatous or tuberculoid cases, but those in which no macules or infiltrations are seen, but in which bacilli remain in the nerves and have not burst into the corium of the skin. Such cases are divided into three groups but no clinical symptoms are given.

In the section on diagnosis details are given of Wade's slit smear method and of the staining of slides.

Under therapy there is no mention of Hydnocarpus oil. Of the Sulphones the author prefers the parenteral use of 50% aqueous solution of sulphetrone, but also gives details of the oral use of Dapsone. He advises great care in the use of sulphones in dimorphous cases, as serious nerve damage is likely if they go into reaction. The sulphones appear to interfere with the metabolism of the *M. lepræ*, which undergo fragmentation. Khanolkar has shown that as the bacilli first attack the nerves, so finally the nerves act as reservoirs of the granular bacilli, and as the disease may recrudesce from these maintenance doses of sulphones are advised for a prolonged period. G. O. TEICHMANN.

CORRESPONDENCE.

Medical Department,
Headquarters Office,
P.O. Box 8,
Entebbe, Uganda.

The Editor,
Leprosy Review,

13th May, 1954.

Dear Sir,

I have read with interest Sir Leonard Roger's paper on "Leprosy Incidence and Control in East Africa." (Leprosy Review, Vol. 25 1954, No. 1. Page 41). There are certain discrepancies, however, which should be corrected.

Sir Leonard states that in 1931 Uganda received £15,350 in BELRA grants. This, of course, can hardly be true, as BELRA's total income and expenditure that year were less than £6,000. The actual grant was £500.

The reference to Western Buganda is misleading. There were no discussions until 1952. Preliminary negotiations took place in Toro in 1950. Sir Leonard may have inadvertently confused the Kingdom of Buganda with the Protectorate of Uganda, a mistake easily made with those not familiar with East Africa. This is a constitutional distinction of great importance about which the local population is sensitive, and it has been at the root of the widely publicised events of recent months.

The statement that "The Owerri Province of South East Nigeria was selected for a crucial test as the most highly infected extensive area found in British Territory by the British Empire Leprosy Relief a quarter of a century ago with seven times the leprosy incidence of India" is very unexpected. I was the only full time worker in the Owerri Province at that time, and there were no such investigations. The only record available was compiled from answers to a questionnaire. This gave the number of cases as 12,200 in a population of 1,873,320. The only actual incidence figure was one per thousand, as as late as 1936 the Leprosy Review re-produced a map showing the disease as rare or uncommon.

I have heard and seen many references to the origin of this work; they have not all been accurate, nor have they always caught the atmosphere in which the work began. The control scheme was never superimposed to demonstrate a theory, though

it may have been so used. The Owerri Province and Uzuakoli were chosen deliberately with the future in view. Clan settlements had been in existence for some years, even in 1935, and the control scheme was the only logical development of these and of Uzuakoli. I would refer Sir Leonard and any who are interested to the 1935 Annual Report of Uzuakoli which included the first outline of the scheme and was published on the suggestion of the late Sir Walter Johnson then Director of Medical Services under the title " Leprosy in Southern Nigeria. Problems of Treatment and Control " and to Dr. Muir's report of his visit to Nigeria in 1936. No one individual or organisation was responsible for the whole conception or the final structure. It has been a composite co-operative effort to which through the years many have contributed. I hope that a sense of satisfaction will not produce forgetfulness of how, when, why, and at what cost the plan first saw the light of day and under varying influences became translated into reality.

Yours sincerely,

James A. Kinnear Brown.

References: West African Medical Journal, Vol. IX, No. 1, Oct. 1936. Leprosy Review, Vol. VII, No. 4, Oct. 1936.

The Editor,
Leprosy Review,
Sir,

Dr. J. A. K. Brown has been good enough to add some details to the information given in your issue of January, 1954 and to refer to his Uzuakoli report of 1935. Unfortunately, I did not find that report among several hundred annual medical reports of British African Territories of the last thirty years that I was able to study at the London School of Tropical Medicine for the purposes of my paper: the sole object of which was to bring out the cordial " co-operative effort " (to which he refers) which has resulted from the combined work of Colonial Administrative and Medical Officers, medical missionaries, BELRA and Toc H workers towards the gradual reduction of leprosy incidence by modern methods, at which we are all aiming.

Yours faithfully,

Leonard Rogers.