LEPROSY REVIEW

The Quarterly Publication of
THE BRITISH EMPIRE LEPROSY RELIEF ASSOCIATION.

VOL. XXIII. Nos. 3 and 4. JULY-OCT., 1952.

Principal Contents

167 VICTORIA STREET, LONDON, S.W.1

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

LEPROSY REVIEW.

Vol. XXIII, Nos. 3 and 4 JULY—OCTOBER, 1952

CONTENTS

Edited by DR. R. G. COCHRANE, Medical Secretary of the British Empire Leprosy Relief Association, 167 Victoria Street, London, S.W.1, to whom all communications should be sent. The Association does not accept responsibility for views expressed by the writers.

NOTES ON CONTRIBUTORS

DR. JOHN A. DREISBACH is Medical Superintendent of the Sudan Interior Mission Leprosy Hospital outside Kano, N. Nigeria.

DR. A. S. GARRETT is a C.M.S. Missionary, and Area Superintendent in the Onitsha Province, and Medical Superintendent of the Oji River Leprosy Settlement, Eastern Region, Nigeria.

DR. M. G. CORCOS is the Medical Officer at the Oji River Leprosy Settlement.

DR. H. PAUL is the Medical Superintendent of the Lady Willingdon Leprosy Hospital, Chingleput, Madras State, S. India.

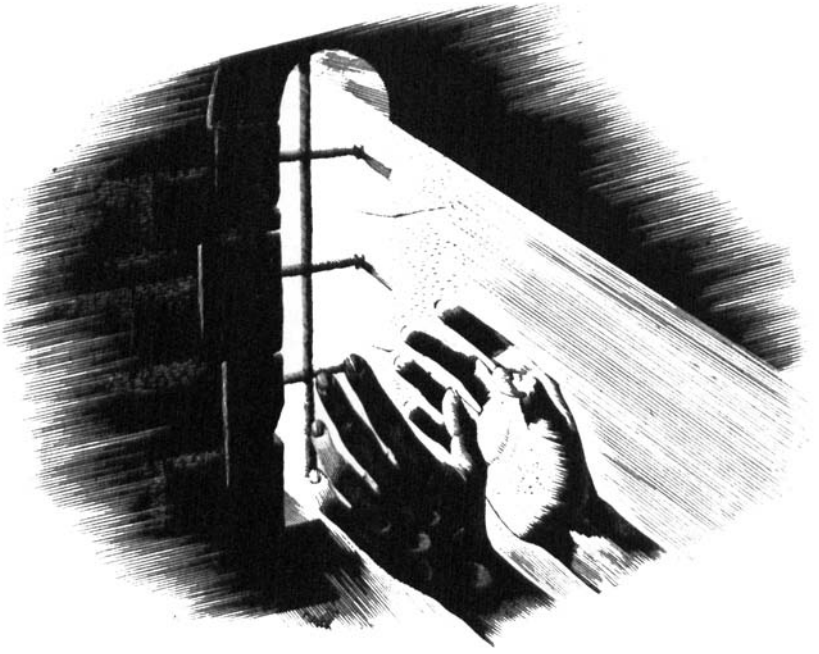
DR. JOHN LOWE is the Leprosy Research Worker under the Nigerian Government, and is stationed at Uzuakoli, Eastern Region, Nigeria.

DR. H. W. WHEATE is working under the British Empire Leprosy Relief Association, and is Medical Superintendent at the Kumi Leprosy Home, Uganda.

DR. K. RAMANUJAM is Medical Officer in charge of the Centre for the study of Child Leprosy at Saidapet, Madras, S. India.

DR. V. R. KHANOLKAR is Director of Laboratories, Tata Memorial Hospital for Cancer at Parel, Bombay, India.

DR. R. G. COCHRANE, in addition to being Medical Secretary of BELRA, is Adviser in Leprosy to the Ministry of Health, London.



Dispel the shadow of leprosy . . .

In the treatment of Leprosy, whether by oral or intramuscular methods, 'Sulphetrone' is the drug of choice. Its proved efficiency and low toxicity place it in a class of its own. In addition to its therapeutic advantages, 'Sulphetrone' is water-soluble; thus, injection is simpler, and more economical than with oil-suspended sulphones.

'Sulphetrone' is issued as compressed products of 0·5 gm. (containers of 100, 500, 1000 and 5000) for oral use; as granules (bottles of 100 gm. and tins of 1 kilo) for the preparation of injection solutions; and as 5 c.c. ampoules of 50 per cent solution (boxes of 100).

'Sulphetrone'
SOLAPSONE

BURROUGHS WELLCOME & CO. (The Wellcome Foundation Ltd.) **LONDON**

ASSOCIATED HOUSES: NEW YORK MONTREAL SYDNEY CAPE TOWN BOMBAY SHANGHAI BUENOS AIRES CAIRO DUBLIN

EDITORIAL

We have considered it expedient to publish a somewhat larger number of the Review by combining the July and October numbers. The difficulties of printing and of collecting articles from many different countries is appreciated by Editors of technical journals, and therefore the necessity for this decision will be understood. The Editor is most grateful for the response which has come for articles, but more material is needed if the Review is to maintain a standard of efficiency which will make it of value, especially to the leprosy worker who is away from centres of research, and is unable to seek the advice of the more experienced leprologist.

One of the main reasons for publishing in one issue both the July and October numbers is the necessity for a considerable amount of travelling abroad by the Editor, as Medical Secretary of the Association. He will shortly be making a tour of East Africa, visiting the Sudan, Uganda, Kenya, Tanganyika, Nyasaland and N. Rhodesia. One of the main objects of this visit is to examine the possibility of a Leprosy Research Unit in the High Commission's Territories, and to choose, in consultation with the Inter-Territorial Leprologist, a site for an institution which could be developed into a research and training centre for East Africa. We therefore publish in this number of the Review an outline of the proposed research scheme. It is accepted that the most practical lines of research are those of Epidemiology, Immunology and Therapy. We feel, however, if leprosy is to be understood adequately, that more detailed research is necessary along the lines of Histopathology and Bacteriology. In any case it is our opinion that a true assessment of the sulphone drugs and new chemotherapeutic and antibiotic agents cannot be undertaken without a study of biopsy material taken at regular intervals from patients under treatment.

It is natural that much of the work on leprosy is concentrated on sulphone therapy, and an increasing number of articles from workers using these remedies over a period of years are being published. We therefore offer no apology for once again devoting a large section of this Review to such articles. Lowe has previously stated that diamino-diphenyl-sulphone (DDS) was excreted in significant amounts in the milk of nursing mothers, and therefore the article by Dr. Dreisbach, of Kano, N. Nigeria, is of particular interest. It has been the universal experience of all workers that

children separated from infective parents at birth, or very shortly after, seldom, if ever, contract leprosy. Nevertheless, it is reassuring to have further evidence that probably a measurable concentration of sulphones (both sulphetrone and the parent sulphone) is present in the tissues of babies on the breast, to give such infants some protection. With this additional precaution one can recommend that babies born of mothers with leprosy should not be weaned, but should be separated from the mother except when the child is put to the breast. A garment preventing contact of the baby with the parent's body should be worn by the mother, and only the nipple should be exposed. With adequate sulphone therapy there appears to be no reason why mothers should not be permitted to feed their infants.

An interesting point arises in Dr. Dreisbach's article, when he states that " It is our opinion, and it has been *adequately substantiated* (italics ours) we feel by epidemiological studies, that all active cases of leprosy are infectious." This raises the question of the infectivity of the case in which acid-fast organisms cannot be found by standard methods of examination. With the newer techniques of staining for acid-fast bacilli in the tissues, and the concentration method described by Dr. Khanolkar in this issue, it cannot be denied that M. leprae can be found in all active cases. Nevertheless to state that such cases constitute a public health danger seems, on all evidence available, rather an exaggeration.

We believe that if careful search could be made, and this is often impossible, for the latent period of leprosy is so long, that in all cases the open contact would be discovered. Further, it is probable that open cases visiting houses for a few nights would constitute a far greater danger to the household than a closed case living in the same house. In one instance it took fifteen years to trace an open contact of a closed case isolated in a leprosy hospital in India, and the lepromatous contact was discovered in this country! We would therefore urge great caution before too much stress is laid on the possible infectivity of the closed case, for all schemes so far devised in which the open case has been adequately isolated point to this measure as being effective in the control of the disease. Evidence of this statement we hope to produce in a future issue of this Review.

The article by Dr. Garrett and Dr. Corcos gives further evidence that unless very carefully administered, even in the small dosages advocated, serious toxic results may be occasionally encountered on giving the mother-sulphone. We draw our readers' attention to

their article, and would remind them that in areas where the lepromatous rate is high (30-40%) these toxic accidents are liable to be somewhat greater. It is a logical argument to state that a minimum of toxicity is a price worth paying for DDS, but it must be admitted that toxic signs do occur, and occasionally these are of a serious nature. No adequate comparison of an equivalent number of cases on DDS and on aqueous sulphetrone has yet been published, but as far as we know the latter remedy has never shown serious hepatitis, renal damage or psychosis, and there is at least an alternative to oral Dapsone. Admittedly this substance has to be given by injection and is somewhat more expensive than the parent sulphone. The present annual cost of aqueous sulphetrone, at 3 gms. a week, is 14/6d.; at 2 gms. a week, which appears to be an effective dose, it is 9/6d., as compared with 11/- with Dapsone on a dose of 800 mgm. per week.

Dr. Lowe's article on Agranulocytosis during the administration of Thiasemicarbazone is a salutary reminder that modern chemotherapeutic remedies have their dangers as well as their advantages. It would be well for those administering thiosemicarbazones to be watchful for these complications. Our opinion with regard to sulphone therapy has now been fairly well formed. For convenience and cheapness DDS (Dapsone) is the choice, but it is not free from toxic signs, some of which are serious and possibly fatal. In mass therapy, where there are dangers of over-dosages due to misuse of the drug, or when therapy cannot adequately be controlled, we believe it is safer to administer aqueous sulphetrone (50% solution) parenterally. In cases of toxicity due to DDS, thiosemicarbazone does not seem to be a wise alternative because there is evidence that it too is a hepatic poison. We again believe in such instances parenteral sulphetrone is the alternative, unless the newer remedies, such as isonicotinic acid hydrazide, prove to be effective—there is no adequate clinical evidence of this as yet.

Dr. Wheate's article on leprosy control raises many points and it will be of great interest to follow the work in East Africa, for here again is an area where control of leprosy on a wide scale seems possible. We welcome particularly Dr. Wheate's emphasis on the need for preventive measures, for we feel that without adequate emphasis on the need for prevention, our new and powerful therapeutic weapons will have much less chance of success. This point is well illustrated in the Eastern Province of Nigeria where largely as a result of clan segregation centres set up by Dr. Davey nearly twenty years ago, leprosy as a serious endemic disease has ceased to exist. It should be mentioned in this connection that sulphones

were introduced on a wide scale only a couple of years ago, and therefore are only responsible for a more rapid decline of the curve of incidence. Without sulphones leprosy it is believed would have been controlled in this area. With sulphones confidence has been established, and the day when leprosy is no longer a public health problem has been measurably hastened.

The article by Dr. H. Paul on the negative rate in persons treated with sulphone therapy over a period of 4 years, suggests that in Madras, with all forms of treatment, the number of negative cases is approximately 40%. The work of Khanolkar on examination of tissues for acid-fast bacilli, both in section and by special concentration methods, described in this number, raises the question as to whether a person can be completely freed from all organisms. If in addition credence is given to the work of the Swedish bacteriologists, Reenstierna and Hallberg, then the possibility that the M.leprae may revert in the tissues to a relatively virulent non-acid fast fungus form, must be seriously considered. In passing, it may be of interest to mention that these workers detected such forms in a nerve in which there were only the remnants of a few acid-fast granules. The case had been negative for two years and had been given sulphone therapy. All these questions raise research problems of the greatest interest. We are aware that negative rates of 90% have been recorded elsewhere over a six-year period, but there are so many factors, e.g. severity of type, race of the patients, methods of assessing negativity etc., that it is difficult to make a comparison between workers in different countries investigating remedies under vastly different conditions. While we firmly believe that in a period of six years the great majority of lepromatous cases should become negative under standard methods of examination, we must not lightly pass over the possibility of degenerate and other forms of M.leprae remaining in the tissues, from whence a recrudescence of the disease may arise later. Hope there is, great hope, for those who suffer, but this hope must be tempered by reasonable caution, lest the victory so near approaching proves to be a pyrrhic one.

REFERENCES

LOWE, JOHN, Studies in Sulphone Therapy. Lep. Review, **23**, 4.

REENSTIERNA, JOHN. A Fourth Orientation on the Therapeutic Value of an Anti-Leprosy Serum. Int. Jl. Leprosy, **5** (1938), 77.

REENSTIERNA & HALLBERG. Personal Communication (1952).

SULPHONE LEVELS IN BREAST MILK OF MOTHERS ON SULPHONE THERAPY

JOHN A. DREISBACH

Of the many sociological problems that arise in the treatment of people with leprosy, one of the most difficult is that of the care of uninfected children of infected parents. In some places the problem is ignored entirely, and the children are left with their parents, there being no attempt whatever to separate healthy children from active cases of leprosy. There are many attempts at partial isolation. The ideal, however, is complete segregation, examples of which are the Preventoria of Brazil (1, 2, and 3).

There have been many detailed epidemiological studies (4) which have presented evidence which few leprologists will question. The most notable and thorough, perhaps, are those which have been carried out in the Philippines. Briefly, some conclusions are: (1) children are much more susceptible to infection than adults; (2) leprosy is almost always contracted in early childhood; (3) leprosy is not inherited, nor it is an *in utero* infection; (4) and if a new born infant is removed at once from its infected mother and has no contact with an active case, the child will not develop leprosy.

After a study of these findings, it is evident that the ideal way to prevent the children of parents with leprosy from contracting the disease is to remove the children from their parents at birth and to care for them in nurseries or preventoria. This is what is being done in the Kano Leprosy Settlement of the Sudan Interior Mission in Nigeria. At this Leprosy Settlement we have two baby homes, which we call "creches." In one creche we have the children who have been delivered in the Settlement. When the expectant mother is near term, she is admitted to the maternity building, where she stays until after she delivers her child. At the time of delivery, she is attended by the missionary doctor or, in his absence, by a missionary nurse. This delivery is carried out under sterile conditions and the new born infant is taken immediately to this creche, which is under the supervision of a woman missionary and a staff of African nurses who have never had leprosy. The baby is put on a formula which is altered according to weight and age, and as it develops, supplemental feeding, vitamins and an antimalarial drug are added at the recommended times. This system has proved satisfactory, but, as it requires more staff and costly feedings, it is expensive compared with the practice of allowing the mothers to nurse their children. It is gratifying, however, in that none of our children thus raised has ever developed leprosy.

Before proceeding to the main study to be presented in this paper, we shall complete the description of our creche system. The second baby home at our Settlement is referred to as the ' contaminated creche." To this home are admitted the children who accompany their parents to our Settlement, but who on clinical and laboratory examination have no evidence of the disease. These children have had contact with active cases of leprosy for varying lengths of time and have had opportunity to become infected. At the time of admission, they show no clinical evidence of the disease but they may do so later. These children are kept under constant observation and if any clinical manifestation of leprosy develops, they are transferred to the Settlement and active treatment started. It is interesting to note that a child taken away from its source of infection seldom develops clinical leprosy. Since these children are potentially infected, they are kept separated from the children in the other creche.

In some institutions the care of the healthy child will vary with the type of disease of the parents. Often only the children of lepromatous, or so called open, infectious cases of leprosy are cared for in a preventorium; whereas, the tuberculoid or so called closed, non-infectious cases are permitted to keep their children. It is our opinion, and it has been adequately substantiated, we feel, by epidemiological studies, that all active cases of leprosy are infectious, although there are marked degrees of infectivity. Thus we treat all of our children alike regardless of the classification of leprosy into which their parents may fall.

It is evident that such a system as we have described, even though it is what we feel to be scientifically correct and ideal, causes new sociological problems. The mother has no part whatsoever in the care of her child and often loses interest in its development. This is not good for either the child or the parents, for the ultimate goal is to re-unite the family when the parents' disease becomes arrested. It was with a twofold purpose that we started the study to be described—to make the mother feel that she was having an active and vital part in the raising of her child and to cut down the cost of feeding, a problem facing every missionary working on a limited budget.

At first, the mothers' breasts were pumped by an attendant but later they were taught to carry out this procedure themselves at regular intervals during the day. They brought their milk to the creche where it was sterilized by boiling and then bottle fed to their babies, their feedings being supplemented by the stock formula. This proved to be a satisfactory plan. The mothers were happy and took greater interest in their children, and the children

actually seemed to do better even though the volume of mother's milk they received was not nearly enough to meet their daily requirements.

It was about this time that the author attended the Nigeria Central Leprosy Advisory Board Meeting, where during the proceedings the problem of the prevention of leprosy was discussed. One government leprologist suggested the possibility that mothers with leprosy who were being treated with sulphone drugs might possibly be secreting enough of the sulphone in the breast milk to act as a prophylactic dose to the nursing children. Questioning such a possibility and reviewing the available literature, however, revealed that little was known concerning the secretion of sulphone in breast milk. If it were secreted in breast milk, was there enough to cause an appreciable blood level in the nursing child, would it be enough to act as a prophylactic?

Answers to these questions could prove very interesting since if prophylaxis could thus be obtained, we could do away with the very expensive creche system, and still know that we were preventing the healthy children from developing leprosy. Many problems could thus be solved and considerable money saved.

The following study was an attempt to answer some of these questions:

At the time of this study, there were at the Kano Leprosy Settlement six mothers who were bringing their milk to the creche for their babies. All these infants were less than three months of age. Five of these mothers were on sulphetrone treatment. They were receiving this drug twice weekly by I.M. injection of 50% aqueous solution. The sixth was on oral diaminodiphenyl sulphone twice weekly. The dosage of these drugs had been regulated by weekly hemoglobin determination and monthly blood sulphone levels as well as by clinical observation.

All the mothers were given a week's rest from treatment in order to bring their blood level to zero as a base line for this study. They were then given 10 c.c. of a 50% aqueous sulphetrone solution I.M. (5 gms. of sulphetrone) and blood sulphetrone determinations were taken before treatment and at 2, 4, 6, and 24 hours after treatment. The sixth mother was given 0.5 gms. of diaminodiphenyl sulphone orally and diaminodiphenyl sulphone blood level was taken at the same intervals. At the same time, samples of breast milk were taken before and at 4, 6, and 24 hours after treatment. These time intervals were chosen because we had shown by studies in our own laboratory, and had read reports by other investigators, that we could expect the peak blood level at about 2-6 hours after treatment, the level gradually returning towards the base line over the next 72 hours.

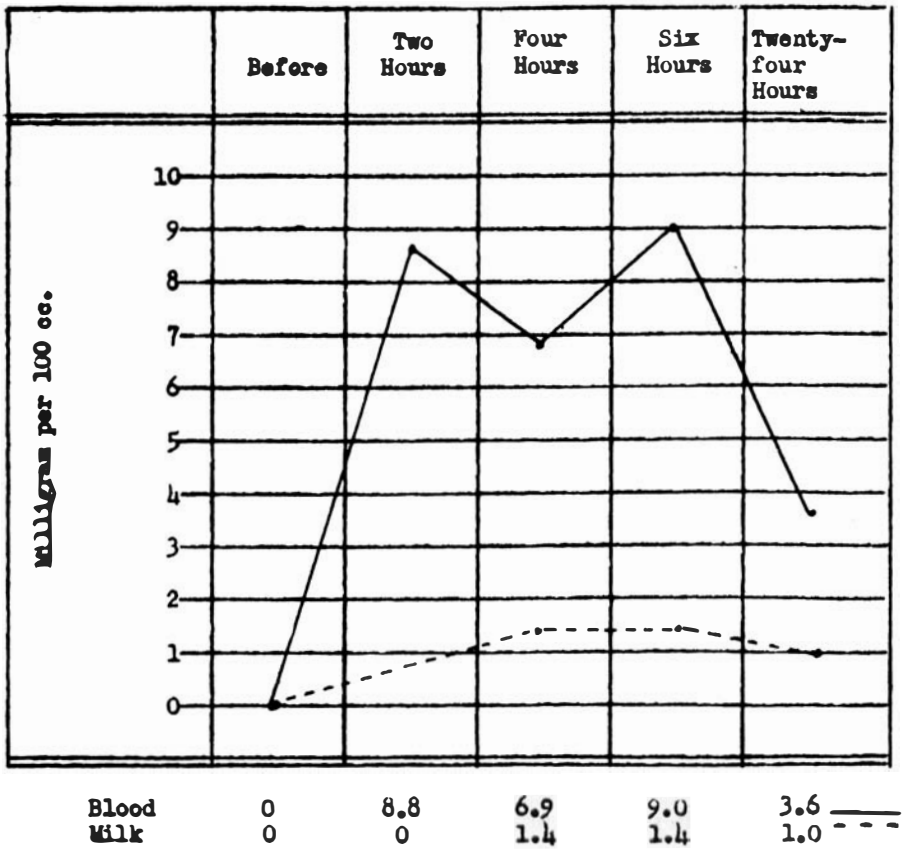
These studies were repeated on two occasions several weeks apart and the accompanying graph represents an average of the findings of these studies:

The blood sulphetrone levels were determined by the Branton Marshall (5) method, using the Loviband comparator. The blood diaminodiphenyl sulphone level was determined also by the Branton Marshall (6) method, using a known standard for a control and using the Kelt-Duboscq colorimeter for comparison.

The sulphetrone and diaminodiphenyl sulphone levels of the breast milk were determined the same way. There were some technical difficulties encountered which took some time and minor modification of technique before we could obtain a clear solution for colorimetry. After we had worked out those modifications, however, we were able consistently to obtain a clear solution and attain consistent readings.

A study of the graph will reveal that there is an appreciable

Curve showing levels of Sulphetrone in Blood and Milk



amount of sulphetrone excreted in the breast milk. More detailed studies, not being reported in this paper, led us to believe that the peak of milk sulphone was about six hours after treatment, and that it appeared more slowly and returned to the base line more gradually, but sooner, than the blood sulphone level.

In the light of these studies we now know that mothers on adequate sulphone therapy did secrete definite, measurable amounts of the respective sulphone drugs.

The next step was to find if the infants fed on breast milk from mothers receiving sulphone therapy ingested enough of the milk sulphone to have a measurable blood sulphone level.

For this part of the study, we chose the following method: The mothers' breasts were pumped six hours after treatment and the milk after sterilization by boiling was bottle fed to their infants. We should expect to find the highest milk sulphone content in this specimen of milk. We had planned to do repeated vein puncture on these infants and run blood sulphone levels on the samples. In view of the fact that these infants were all small, however, and repeated vein punctures were not only difficult but possibly deleterious, we altered our plan to that of collecting urine from the infants. This was much easier and of no harm to the infant. We took urine specimens four hours after ingestion of the breast milk, and the respective sulphone urine levels were determined. An average of these determined was 2.6 mgms. per cent. Although we do not know what the sulphone blood levels were in these infants, we do know that a very definite and measurable amount was excreted in their urine. It is conceivable that these blood levels, even though they undoubtedly were low and much under the optimal therapeutic level, might possibly be of prophylactic value. The actual evaluation of such a possibility is a study that will take years of observation and study fraught by many difficulties, and also possibilities of error. For example, the child in our country is weaned at 2 years of age, at which time he no longer would be getting sulphone from his mother. Of course, by that time his mother might be arrested and the problem no longer exists. But even at best, it would take 10-20 years of observation to know if these children later developed the disease, and in our country where follow-up studies are often difficult, there is the possibility of losing track of many cases. At best, it would take a great deal of very wise and unbiased judgment properly to evaluate the findings.

I do not feel that the many difficulties encountered in such a long time study should deter us from embarking on it, for it is the only way we will be able to answer the question of prophylaxis in the prevention of leprosy.

SUMMARY AND CONCLUSIONS

A study has been reported in which an attempt was made to answer some questions relative to the possibility of nursing infants receiving enough sulphone in breast milk, from mothers with leprosy on sulphone treatment, to act as a prophylactic in the prevention of leprosy.

1. Nursing mothers on adequate treatment with sulphone do secrete measurable amounts of the sulphone in their breast milk.

2. Infants fed on this milk obtain enough sulphone to cause it to be excreted in their urine in measurable amounts.

3. The final answer to the problem of prophylaxis will come only after long study and the solution of many difficult problems.

1. Weaver, E. (1940). Int. J. Lep. 8, 495.
2. Weaver, E. (1945). Leprosy Review, 16, 40.
3. Weaver, E. (1948) Memoria, V. Congresso Internacional De La Lepra.
4. Lara, C. B. Memoria, V. Congresso Internacional De La Lepra. 414 pages.
5. Brownlee, G., Green, A. F., and Woodbine, M. (1948). British Journal of Pharmacology. 3.
6. Branton, Marshall (1939). Journal of Biological Chemistry. 128. 537-550.

DAPSONE TREATMENT OF LEPROSY

A. S. GARRETT and M. G. CORCOS

The following is a summary of 22 months experience of treatment of 10,000 patients with leprosy by Dapsone (D.A.D.P.S.) administered by mouth.

Treatment has been carried out in a central settlement of about 1,000 patients and in 27 out-clinics, increasing during the period under review, to 39.

Within the first 4 months those on treatment had reached about 5,000 and the total number has exceeded 10,000. During the period the medical staff has consisted of one to three doctors and one to six qualified nursing staff. The bulk of the work has fallen on lay workers who have been trained for the purpose.

At the beginning all settlement patients were treated 6 days a week with a maximum dose of 0.2 gm. daily. The out-patients and patients in segregation villages were treated twice weekly with a maximum dose of 0.4 gm. After 6 months, it was apparent that, with the medical supervision available, the latter course gave much less complications. In *Leprosy Review* July-October, 1951, the routine treatment and early complications have been described. This present article gives more details of the effectiveness of this treatment and further details of all complications.

2. Effectiveness of treatment.

CLINICAL.

Nearly all tuberculoid cases are much improved. Lesions become flattened and about 60% of them regain their colour within 18 months or so of starting treatment. The colour is more quickly regained in those lesions exposed to the sunlight. Also, as a general rule there seem to have been more rapid progress in those who have never had hydnocarpus oil than in those previously treated with it.

There remain a large group of patients whose macules appear completely flattened or wrinkled but in which the normal pigment has not returned or has returned only partly. Among these there are many who, near the beginning of treatment had new tuberculoid macules which have now subsided.

About 10 to 15% of tuberculoid cases show continuous mild activity up to the present time. The macules remain slightly raised, but are not advancing.

About a dozen have had tuberculoid reactions of considerable proportions with increase of paralysis and deformity. Apart from these cases, nerve signs in tuberculoid leprosy have been absent or almost so.

In patients with lepromatous leprosy the improvement has been satisfactory. The great majority have improved without incident apart from very mild lepra reactions. About 10% have had repeated lepra reactions and a further 10% have had repeated nerve reactions. In many of these, the dose has been reduced for a few months with satisfactory results. In others, removal of the nerve sheath has been followed by great improvement. 15 out of about 1,500 lepromas have been changed to thiacetazone treatment because of repeated reactions. Eye reactions have been rare and controlled by temporary reduction of dose, but 5 have been transferred to thiacetazone treatment.

3. Bacteriological.

In nearly all cases the bacterial improvement has been steady

and well marked. As a routine 3 smears are taken and the result is tabulated as −ve to 4+ thus the maximum Bacteriological Index (B.I.) for a patient is 12.

The following is a group picked at random from several segregation villages to indicate the improvement.

Pt's No.	B.I 1950	B.I Last Smear	Pt's No.	B.I 1950	B.I Last Smear	Pt's No.	B.I 1950	B.I Last Smear
AM 50	9	2	J 220	2	0	D 825	6	1
,, 68	7	3	J 2361	12	10	D 884	7	4
,, 70	8	4	AN 23	5	6	D 887	2	1
,, 127	8	0	AN 107	3	0	D 1081	5	0
,, 137	7	4	AN 112	3	0	D 1158	12	11
,, 146	5	1	D 96	2	0	G 111	10	6
,, 162	9	5	D 132	8	1	G 137	2	0
F 79	2	2	D 236	7	3	G 176	2	1
F 117	3	4	D 442	4	1	G 227	5	2
F 229	3	0	D 538	4	5	G 428	2	3

4. Trophic lesions.

New trophic lesions have been uncommon but there is no evidence that dapsone has any considerable effect on existing trophic lesions. Gangrene, ascending from a trophic ulcer has been much rarer than under hydnocarpus oil. This may be due to the control of the bacteria of sepis by the dapsone.

5. Drug Intolerance.

The general health of the patients is much improved, but a few have shown signs of intolerance. Dermatitis has affected 2 to 3% of patients; this is often accompanied by enlargement of the liver and occasionally by jaundice. As previously reported 4 died out of the first 2,000 treated. Two have subsequently died. About 10 have proved very difficult to desensitise and 4 of these have been transferred to thiacetazone treatment. In many cases the leprosy has markedly improved after an attack of dermatitis and in some the signs of disease have completely disappeared. These, if difficult to desensitise, have been discharged from treatment rather than risk a renewal of drug sensitivity, but one such patient has renewed tuberculoid activity.

Psychosis has affected about 50 people. Most of these were from among the 1,000 patients who received daily treatment for the first 6 months, though cases are still occurring. Six have had psychotic symptoms for several months and appear likely to continue. The others have recovered after 2 or 3 months off treatment, after which treatment has been renewed.

ACUTE AGRANULOCYTOSIS CAUSED BY TB1/698 (PARA-ACETAMIDOBENZALDEHYDE THIOSEMICARBAZONE)

JOHN LOWE

The use of TB1/698 in leprosy has been described by Hohenner (1949) Grosch and Kaliebe (1950) Walter (1950) Ryrie (1950) Schneider *et al* (1950) Vegas *et al* (1950) and Lowe (1952). The earlier reports dealt with one or a few cases treated for short periods. My previous report dealt with 126 cases treated for periods up to seventeen months.

The present report is not concerned with the value of TB1 in leprosy, which was dealt with previously. It is concerned with the occurrence of acute agranulocytosis during the administration of this drug.

Specific toxic effects of TB1. Many reports of the toxic effects of T.B.1 have been published. The early German work on the use of TB1 in tuberculosis was done with doses much higher than those now used, and toxic effects were more common and serious than now. Even with the lower doses at present used, some workers, particularly in the United States, regard the drug as too toxic for the treatment of tuberculosis: but that is not the opinion of the majority.

The effects recorded included anorexia, headache, epigastric discomfort, vomiting, and other evidence of disturbed liver function; fever and rashes; a mild haemolytic anaemia; and agranulocytosis (rarely). Thus there is evidence of damage to the liver and to the bone-marrow.

In 146 cases treated for periods up to 21 months, the only serious toxic effect has been an acute agranulocytosis which has been seen in three cases, associated in one case with hepatitis and jaundice.

Case records.

(1) A young man, in good physical condition, with tuberculoid leprosy, was treated with T.B.1 50 mg. a day for the first week, 100 mg. a day for the second week, and thereafter 150 mg. a day. At the end of five weeks treatment, he appeared one morning complaining of malaise, and pain in the teeth. That afternoon his temperature was 103°F; he was ill and toxic, and his tooth sockets, tonsils, fauces, and the nail beds of the toes were acutely inflamed. An acute agranulocytosis was diagnosed and confirmed by blood examination, and intensive penicillin treatment was instituted,

1,000,000 units of procaine penicillin in oil being given each day. The clinical condition subsided in three days, except that small necrotic areas on the toes took several weeks to heal. The white-cell counts before treatment started and during and after this incident are shown in the accompanying table.

The striking features were a decrease of more than 90% in the total granulocytes; a decrease of 82% in the polymorphs, with a return to the previous figure in a week; and the almost complete disappearance of eosinophils, which had previously been very numerous (associated with filariasis due to Acanthocheilonema perstans), and their failure to reappear until the third week.

(2) A young African man in good physical condition, with mild leprosy, started T.B.1 treatment on February 9th, 1952; the dosage was 50 mg. a day for one week, 100 mg. a day for the second week, and 150 mg. a day for the third week. On the twenty-second day of treatment he felt unwell and feverish in the evening, and next morning he reported with a temperature of 101°F. Malaria was suspected, but a blood-film revealed acute agranulocytosis. T.B.1 was stopped, and 1 million units of penicillin was given and was repeated daily until recovery. Pentnucleotide was not available.

That afternoon the temperature rose to 105°F. There was no serious inflammation of the mouth or throat; there was a small septic focus on one foot at the site of a cut, and later a similar focus appeared on one hand.

A remittent fever continued for seven days, reaching its maximum, 106°F, on the second day and then slowly subsiding. During this time no serious local inflammation developed any where, and the general condition of the patient remained fair, but toxaemia was marked. The spleen became palpable on the fourth day.

At the eighth day the penicillin injections were stopped, but almost immediately the fever recurred and a widespread lymphadenitis developed, with suppuration of the femoral glands on both sides; this cleared up with further penicillin treatment and surgical drainage. Smears from the evacuated pus showed staphylococci. During this second period of fever the white cell count was high and many immature cells (myelocytes and metamyelocytes) appeared in the peripheral blood. Thereafter the patient made an uninterrupted recovery and has since been treated with diamino-diphenyl sulphone with no complications.

(3) A well nourished young man with moderately severe leprosy started treatment with TB1 on Jan. 29/1952, the dose being 100 mg. a day for three weeks, and 150 mg. a day thereafter.

On March 13th after six weeks treatment he became ill with some fever but no obvious cause. There was no local symptom of any kind, and the blood showed no malaria parasites. The polymorphonuclear count was low; agranulocytosis was suspected and daily blood counts were made; five days later agranulocytosis was definitely diagnosed, so TB1 treatment was stopped and penicillin treatment was instituted. During the next two days the fever fell, but the spleen and liver became enlarged, and jaundice developed. Later the fever subsided and the granulocytes returned, but the liver was enlarged down to the umbilicus, and was very tender. Later the jaundice became intense, although the patient's general condition remained good. All the usual laboratory tests for a toxic hepatitis gave positive results. During the next ten weeks, with no specific treatment, the hepatitis and jaundice slowly subsided. Treatment with diamino-diphenyl sulphone has just been started.

Period of T.B.1 treatment	**Case 1 5 weeks**	**Case 2 3 weeks**	**Case 3 6 weeks**	Notes
Total count before treatment	10,300	6,500	8,500	
Granulocytes ...	5,900	3,200	4,240	
Day of illness 1	3,300	1,800	4,800	In cases 1 & 2 TB1 treatment stopped.
Total count and granulocytes ...	500	180	1,100	In case 3 continued
Day 2	3,500	1,300	6,700	
	500	110	2,000	
Day 3	3,000	1,900	7,000	
	600	140	1,500	
Day 4	3,700	2,300	—	
	800	120	—	
Day 5	—	2,000	7,800	TB1 stopped in case 3.
	—	40	250	
Day 6	4,200	4,200	7,900	
	1,900	430	230	
Day 7	4,500	8,500	6,200	Many myclocytes & metamyclocytes present in case 2.
	1,900	2,550	120	
Day 8	6,000	10,000	5,600	,,
	600	5,230	450	
Day 9	6,500	10,100	8,400	,,
	2,900	6,190	1,600	,,
Day 10	6,000	17,900	7,300	,,
	2,200	12,940	2,400	
Day 11	6,200	15,600	—	
	3,000	12,000	—	
Day 12	—	17,800	—	
	—	13,600	—	
Day 18	—	7,100	—	
	—	5,250	—	

Discussion.

First arises the question of the diagnosis and causation. The white cell counts recorded in the table leave little doubt of the accuracy of the diagnosis. In case 1 the granulocytes fell from 5,900 to 500; in the second case from 3,200 to 40; and in the third case from 4,240 to 120. In all three cases the granulocytes began to increase within a few days of the cessation of TB1 treatment and of the institution of penicillin therapy. These three cases, and a fourth mild case recorded below, all occurred among 146 patients treated here with TB1; in some hundreds of other patients treated with other remedies for leprosy, no such case has been seen in several years. It appears certain that the cases were cases of agranulocytosis caused by the administration of TB1.

In all cases the agranulocytosis occurred during the first few weeks of treatment, and it is a striking fact that in 21 months treatment in 143 cases we have not seen agranulocytosis occurring later than the 6th week. It appears definite that agranulocytosis occurs early or not at all. This finding supports the idea, expressed by some other workers, that this agranulocytosis is an allergic rather than a toxic phenomenon, and is not attributable to the cumulative toxic action of the drug. Because there is another effective treatment (diamino-diphenyl sulphone), TB1 treatment has not been resumed since agranulocytosis occurred, although there is reason to believe that it could be resumed at low initial doses and with a gradual increase. In this connection, a fourth mild case in the present series may be quoted.

A young man with mild leprosy started TB1 treatment on March 20/1951. His granulocytes on that date numbered 2260 out of a total count of 4,700. After 23 days treatment with 100 mg. a day, he felt slightly unwell and had slight fever, and his granulocytes had fallen to 660 out of a total count of 3,000. Treatment was continued; three days later his granulocytes numbered 1430, and next day 2100; thereafter the number was steadily over 2000. This was apparently a mild agranulocytosis, which once again occurred in the first few weeks of treatment, and which subsided in spite of the continuance of TB1. Further, he has now completed 15 months treatment with no sign whatsoever of recurrence of the agranulocytosis. One would perhaps not recommend the continuance of TB1 treatment in an established case of agranulocytosis, but the above facts throw light on the causation and nature of agranulocytes, and suggest an allergic and not a true toxic phenomenon.

Nevertheless, as is well known, acute agranulocytosis can be very fatal, and our finding of 3 cases in 146 treated means that

the danger is a very real one. In cases 1 and 2, prompt diagnosis and penicillin treatment quite possibly saved the patient's life. The findings in case 2 indicated the occurrence of an acute staphylococcal septicaemia; probably a similar factor was present in the other cases.

Regarding diagnosis. Only in case 1 was there inflammation of the mouth and throat which are the classical signs of acute agranulocytosis. In cases 2 and 3 there were no localising signs to begin with, but merely fever with chills which naturally suggested malaria in this malarious country. In all three cases the agranulocytosis was detected in the thin and thick blood films prepared for examination for malaria parasites. In these films agranulocytosis is best detected by the use of the 2/3rd objective and a high power eye piece. These facts emphasise the importance of keeping an open mind and being prepared to find something quite different from what is expected, and of examining specimens with the low power of the microscope before using the oil-immersion lens.

One may formulate a general principle. In patients receiving treatment with thiosemicarbazones, any fever occurring during the first few weeks of treatment should be regarded with grave suspicion, and the blood should be examined for evidence of agranulocytosis.

Finally, regarding treatment of agranulocytosis, it may be said that penicillin in adequate doses has given very satisfactory results. If infections can be controlled, the granulocytes will look after themselves. No pentnucleotide was available, and none appeared to be needed. The speed of recovery from agranulocytosis under penicillin treatment was very striking in all three cases. In all three cases the granulocytes had returned in considerable numbers, with counts over 2000, within 9 days of the institution of penicillin treatment.

The hepatitis seen in one of the three cases was apparently a toxic hepatitis showing little or no connection with the agranulocytosis which accompanied it. It took many weeks to subside. Hepatitis has been recorded as a not infrequent toxic effect of TB1.

Summary and conclusions.

In 146 patients with leprosy treated with TB1 three severe and one mild case of agranulocytosis have been seen. In all four cases, the agranulocytosis occurred between the third and the sixth weeks of treatment. In the three severe cases, typical findings in the mouth and throat (" agranulocytic angina ") were found in only one. The symptoms were of fever with chills and strongly suggested malaria. In one case a staphylococcal septicaemia was present. Probably a similar factor caused the fever in the other two.

The total and differential counts before TB1 treatment and during the attacks of agranulocytosis are presented, and show a marked fall in granulocytes, the lowest figure recorded being 40 per cubic millimetre. The cessation of TB1, and the initiation of penicillin therapy was promptly followed by a fall in the temperature and the return to normal of the granulocyte count.

The findings are interpreted as indicating that the agranulocytosis was caused by TB1 and that it is an allergic rather than a true toxic phenomenon, for no case of agranulocytosis has been seen in the many patients who have had from 2 to 21 months continuous treatment with TB1, or who have been treated with sulphone.

The occurrence of such a serious complication of TB1 therapy in 3 of 146 cases treated indicates that the treatment can be used with safety only where adequate facilities for the detection and treatment of agranulocytosis are available. Every fever occurring during the first few weeks of TB1 treatment should be viewed with grave suspicion, and the blood should be properly examined for agranulocytosis. However the excellent response to treatment for agranulocytosis seen in all three cases indicates that, with proper facilities, TB1 treatment is not too dangerous to use.

The danger however is real, and the scope for TB1 treatment of leprosy must be a limited one, for in many countries where leprosy is common, medical and laboratory supervision of treatment is often difficult and sometimes impossible. For use in such areas, sulphone treatment is considered much safer. Moreover there is no clear indication that TB1 treatment is more effective than sulphone, though there are cases in which it is better tolerated.

Acknowledgments.

Thanks are due to Miss F. McNulty, Laboratory Superintendent, for the white-cell counts, and to the Inspector-General of Medical Services (Dr. S. L. A. Manuwa) and the Leprosy Adviser (Dr. T. F. Davey) for permission to publish.

REFERENCES

GROSCH, W., and KALIEBE, H. J. (1950) Zbl. Haut u. GESCHL-Kr. **9** p.1.

HOHENNER, K. (1949) Med. Klin. **44** p.1378.

LOWE, J. (1952) Lancet I p.436.

RYRIE, G. A. (1950) Lancet II p.286.

SCHNEIDER, J., LAVIRON, P., LAUREL, L., BASSET, A. (1950) Bull. Soc. Path, exot. **43** p.733.

VEGAS, M., CONVIT, J., MEDINA, J. A., DE BLOMENFIELD, E. (1950) Int. J. Leprosy, **18** p.451.

WALTER (1950) Z. Hals,—Nas,—u. Orenheilk **2** p.218.

RESULT OF ANALYSIS OF SULPHONE NEGATIVE CASES OVER A PERIOD OF 4—6 YEARS

H. PAUL.

Much has been written since the advent of sulphones in the treatment of leprosy, and over the years since its first inception in the year 1946 in the Lady Willingdon Leprosy Sanatorium, Chingleput, under the guidance of Dr. R. G. Cochrane, a number of sulphone derivatives, and the basic substance itself, have been under trial. These drugs have been administered both orally and parenterally.

This paper deals with the negative rate of sulphone treated cases who have been rendered symptom free and bacteriologically negative, and have remained so for an average period of six months. The average dose of drug and the average length of treatment that was necessary to render a case bacteriologically negative (Appendix I will be helpful to illustrate this) has been calculated.

Tables 1, 2, 3 and 4 give the details of each one of the negative cases under the various sulphone derivatives.

When sulphones were first claimed to be useful in the treatment of leprosy, workers in the field naturally adopted the rational of massive therapy, as is advocated for sulphonamide medication, so as to control the infection in the shortest period of time without giving the infecting agent time to assume resistant forms.

Here at this institution we have learnt to our cost, though no patients died, that massive dosage serves no more useful purpose than the very minimal average dose, which eliminates as far as possible the provocation of toxic symptoms. While it is true from our experience that we initially used relatively high doses of the sulphones, yet one interesting fact emerges, that it is not the quantity of drug that appears to be of importance, but the duration of regular treatment that is essential if satisfactory results are to be obtained. It appears that it will take not less than $2\frac{1}{2}$ to 4 years for moderate lepromatous cases to become negative in any appreciable numbers. Further it will be seen that the different forms of sulphones have produced almost the same negative rate in about the same period of time. It is, however, my opinion that any sulphone in oil dispersion is superior to the soluble and the oral sulphones. Again, from the economic point of view, the basic sulphone in whatever form it is used is the cheapest.

APPENDIX I.

Statement showing the results obtained in the various groups under Sulphone therapy over a period of 4—6 years.

Group	*Total Lepromatous cases*	*Drug*	*Date of commencement*	*No. Bacterio-logically negative*	*Average dose in Grammes*	*Average length of treatment in months*	*Negative rate*
B1 & G1	28		10- 1-50	9			
B & G	18*	Sulphetrone	9- 7-48	8**	340.28	34	44.5%
E	10*	in	9- 7-48	4**	404.3	38	40%
L	31	Oil 25%	10- 1-50	11			
		D.D.S. in					
A, D & F	28*	Oil 25%	9- 7-48	8**	200.36	40	28.5%
M & N	16*	Reduced from	9-11-48	8**	152.5	34	50%
Q		5cc—3cc—2cc	10-1-50	1			
		Sulphetrone Aquous 50%					
C & H	23*	7cc	9- 7-48	12**	603.75	42	52%
O	18*	7cc	8-11-48	5**	836.2	39	27.5%
P	12*	7cc + I.D.	26- 1-49	4**	647.1	36	33%
R	14*	3½cc + I.D.	26- 1-49	5**	461.85	37	35.5%
S	26*	3½cc	11- 5-49	6**	436.16	33	23%
M1	189	4cc	6- 2-50	62			
N1	94	4cc + I.D.	18- 2-50	40			
I	41*	Diasone	Sept. 46 and Sept. 48	19**	1115.7	43	46%
K	3	Sulphetrone Tablets	16-10-46	1	7998	61	

Note:—* Total No. of cases treated over a period of 4 years = 206
** Total No. of Negative cases over a period of 4 years = 79
Average Negative rate is 38.35% over an average period of 37.5 months.

Sulphetrone in oil.

Group No.	*Date of commence-ment*	*Drug*	*Total dose in grammes*	*Length of treatment in months*	*Bacterio-logical result (5-6 months)*	*Date of Discharge*
G 3	10-7-48	Sulphetrone A. Oil 25%	184	18	Q	13-1-50
G 4	10-7-48	7cc twice a week	225.75	31	Q	7-2-51
G 5	10-7-48	From 6-3-51	429	46		
G 8	10-7-48	Sulphetrone Aqueous 50% 4cc	447	46	N	
B 3	9-7-48	Sulphetrone A. Oil 25% + I.D.	532	46	N	
B 8	23-7-48	7cc twice a week	110	10		2-5-49
B 9	23-7-48	From 5-3-51	525	46	N	
B 10	26-7-48	Sulphetrone Aqueous 50% 4cc	269.5	30		12-1-51
E 2	10-7-48	Sulphetrone H. oil	500	46		
E 3	10-7-48	7cc twice a week	218.75	17	N	7-12-49
E 5	10-7-48	From 5-3-51	510	46	N	
E 9	10-7-48	Sulphetrone Aqueous 4cc	388.5	43	N	11-2-52

N = Negative, that is sixteen smears at monthly intervals. Negative for six months.

Q = Quiescent. Similar number of smears. Negative for 3 months.

I.D. = Intradermal injections.

D.D.S. in Oil.

Group No.	*Date of commencement*	*Drug*	*Total dose in grammes*	*Length of treatment in months*	*Bacteriologic result (5-6 months)*	*Date of Discharge*
A 1	10- 7-48	D.D.S. A. oil 25% + I.D. 5cc twice a week	204	25	N	23- 8-50
A 2	9- 7-48	10-1-50 reduced to 3cc 1-3-51 reduced to 2cc	209	34	N	14- 5-51
A 4	9- 7-48	Now Coconut oil	227	46	N	
D 2	9- 7-48	D.D.S. H. oil 25% 5cc twice a week	140	29		13-12-50
D 10	31- 8-48	10-1-50 reduced to 3cc 1-3-51 reduced to 2cc Coconut oil	203.85	42	N	
F 2	19- 9-47	D.D.S. A. oil 25% 5cc twice a week	310	56	N	
F 3	9- 7-48	10-1-50 reduced to 3cc 1-3-51 reduced to 2cc	142.75	44		21- 3-52
F 4	9- 7-48	Coconut oil	166.25	43	N	2- 2-52
M 1	9-11-48		125	28		2- 3-51
M 2	9-11-48	D.D.S. A. oil 25% + I.D.	60	12	N	13-11-49
M 3	9-11-48	3cc twice a week	130	27.5		25- 2-51
M 5	9-11-48	1-3-51 reduced to 2cc	184	46	N	
M 7	9-11-48	Coconut oil	81	18	N	31- 1-51
M 8	9-11-48		159	46	N	
N 1	9-11-48	D.D.S. A. oil 25% 3cc twice a week	164	46	N	
N 2	9-11-48	1-3-51 reduced to 2cc Coconut oil	153	45	N	4- 4-52

Sulphetrone Aqueous

Group No.	*Date of commence-ment*	*Drug*	*Total dose in grammes*	*Length of treatment in months*	*Bacterio-logic results (5-6 months)*	*Date of Discharge*
D 6	27-7-48	Sulphetrone Aqueous 50%	326	46	N	
F 10	23-7-48	3½cc twice a week	257	46	N	
C 2	9-7-48	+ I.D.	773	46	N	
C 4	9-7-48	From 3-5-41 4cc 50% Aqueous	762	41	N	
H 1	9-7-48		732	46	N	13-12-51
H 2	9-7-48		579	31		
H 4	9-7-48	Sulphetrone Aqueous 50%	580	31	N	
H 8	9-7-48	3½cc twice a week	737	46	N	9- 2-51
H 10	3-8-48	From 3-5-51 4cc 50% Aqueous	782	45	Q	19- 2-51*
H 12	31-8-48		739	45		
H 15	10-7-48		531	46	N	
H 16	9-7-48		447	32	N	9- 3-51
O 1	8-11-48	Sulphetrone Aqueous 50%	609	24	N	
O 2	8-11-48	7cc twice a week	894	42	N	4-11-50
O 3	8-11-48	From 19-3-51	894	42	N	
O 4	8-11-48	4cc twice a week	887	42	N	
O 5	8-11-48		897	42	N	
P 1	26-1-49	Sulphetrone Aqueous 50%	739	40		
P 2	26-1-49	7cc twice a week	724	40	N	
P 3	26-2-49	From 2-3-51	364	27	N	22- 5-51
P 4	26-1-49	4cc twice a week	761.5	36.5	N	13- 2-51
R 1	26-1-49	Sulphetrone Aqueous 50%	337.25	27	N	20- 4-51
R 2	26-1-49	3½cc twice a week	498	39	N	
R 3	26-1-49	+ I.D.	492	39	N	
R 4	5-2-49	From 5-3-51 4cc twice a week	484	39	N	
R 5	26-1-49		498	39	N	
S 1	11-5-49	Sulphetrone Aqueous 50%	232.75	18	Q	7-11-50
S 2	11-5-49	3½cc twice a week	451.25	34.5	N	31- 3-52
S 3	11-5-49	From 5-3-51	483.25	36	N	26- 4-52
S 4	11-5-49	4cc twice a week	483.25	35	N	
S 5	11-5-49		483.25	36	N	
S 6	11-5-49		483.25	36	N	

* Relapsed—5-9-51.

DIASONE.

Group No.	*Date of commencement*	*Drug*	*Total dose in grammes*	*Length of treatment in months*	*Bacteriologic result (5-6 months)*	*Date of Discharge*
1.	1- 8-46		1977	64	N	3- 1-51
2.	19- 8-46		1621.5	54	Q	7- 2-51
3.	19- 8-46		1479.6	53.5	Q	7- 2-51
4.	19- 8-46		1534	61	Q	30- 9-51
5.	20- 6-47		2103.7	59	N	
6.	11-11-46		2012.5	66	N	
7.	6- 1-48		1115.8	24	N	1-12-50
8.	12- 9-46		1067.4	56	N	20- 4-50
9.	23- 9-48	Diasone	1266.3	43	Q	23- 4-52
10.	23- 9-48	Average 4 tablets per day	1315.4	43	Q	
11.	20- 7-48			35	N	8- 6-51
12.	12- 9-46			27	Q	5- 2-49
13.	4- 8-48		857.9	40	Q	4-12-50
14.	23- 9-48		808.5	29	Q	15- 2-51
15.	23- 9-48		817.5	40	Q	4- 2-52
16.	12- 9-46		810	29	Q	25- 2-49
17.	12- 9-46		886.8	29	N	25- 2-49
18.	12- 9-46		655.8	27	N	15-12-48
19.	12- 9-46		768.9	33	Q	11- 6-49
				av. 42.78		
20.	16-10-46	Sulphetrone	7998	61	Q	16-11-51

It is interesting to note that out of the original diasone cases, 19 more became Negative, giving a percentage negative over an average period of 42.78 months.—EDITOR.

Other groups on lower dosages and oral DDS, Contiben and TB1 have not been included in this paper, as the time is too short a period for a report.

CONCLUSION: Though it is obvious that the sulphones have come to stay in the treatment of leprosy, yet many a bacteriologically negative patient still requests the medical man to administer intradermal injections of hydnocarpus oil to hypopigmented patches, which frequently remain as residual after sulphone therapy.

Although sulphones are superior to the old hydnocarpus treatment, it is interesting to note that the period in which negative results are achieved has not been appreciably shortened, at least as far as the early or moderate lepromatous case is concerned.

SUMMARY

1. Result of sulphone therapy over a period of 4—6 years.
2. Theoretical considerations based on facts indicating that the period of regular treatment with sulphone is more important than the dosage or type of drug used.
3. Appendix I giving a tabular statement showing details of various groups of drugs and their average dosages and average period of treatment.
4. Details of the individual negative cases.

ACKNOWLEDGMENT

I am deeply indebted to Dr. R. G. Cochrane for his continued guidance in this work which has made this brief report possible.

REFERENCES

COCHRANE, R. G. (1949), General principles in the treatment of leprosy with particular reference to the sulphones. Leprosy in India, **21**, 83.

IDEM (1949a), Editorial: Sulphone treatment of leprosy. Int. Jl. Lep. **17**, 299.

COCHRANE, R. G., RAMANUJAM, K., PAUL, H., and RUSSEL, D., (1949), Two-and-a-half years' experimental work on the sulphone group of drugs. Lep. Rev., **20**, 4.

DHARMENDRA and CHATTERJEE, K. R. (1947), Treatment of leprosy with the sulphone drugs. Leprosy in India, **20**, 70.

LOWE, J., (1951), Diamino-diphenyl-sulphone in the treatment of leprosy. Lancet, **1**, 18.

MOLESWORTH, D., and NARAYANASWAMI, P. S. (1949), The treatment of lepromatous leprosy with DDS in oil. Findings in 100 cases treated in 1 year. Ibid. **17**, 197.

MUIR, E. (1947), The sulphone treatment of leprosy. Brit. Med. Jour. (Reprinted, Int. Jl. Lep., **15**, 309).

LOWE, J. (1952), Studies in sulphone therapy. Lep. Rev. **23**, 4.

IDEM (1952), Finding of a meeting of leprosy workers concerning sulphone treatment of leprosy.

COCHRANE, R. G. (1951), Chemotherapy in leprosy. Lep. Rev. **22**, 57.

DHARMENDRA (1952), Recent advances in the treatment of leprosy. Leprosy in India **24**, 4.

SOME PRINCIPLES AND SUGGESTED METHODS OF LEPROSY CONTROL IN EASTERN UGANDA

H. W. WHEATE

The two leprosy sanatoria at Kumi and Ongino at present serve approximately half the Protectorate of Uganda, the population comprising tribes of three distinct racial and language groups, each with a different traditional attitude towards leprosy and different social customs relevant to public health control of the disease. The institutions themselves lack many of the amenities essential to modern leprosy sanatoria—there are, for example, no proper hospital buildings, laboratory or infant creche. Plans for extension of the work into the preventive field have been made subject to the provision of these essentials.

Principles of Leprosy control in a primitive Community.

A leprosy sanatorium of itself can have no influence on the incidence of leprosy in the population it serves unless:—

(a) The incidence is so low or the population so few that the vast majority of all infective cases can be accommodated in isolation from children.

(b) The sanatorium becomes the centre for rural preventive work, organising surveys, examining contacts, providing outpatient dispensaries and mass treatment, and disseminating elementary propaganda. The purpose of all these measures is to ensure the isolation either at home (house or night segregation) or in the sanatorium, and the treatment of the infective case at the earliest possible time after recognition of the disease. It cannot be too strongly emphasised that mass treatment alone cannot accomplish this purpose.

It is essential to recognise that in such primitive communities as those with whom we work at Kumi, our first task is to **win their confidence.** If we fail, then the first case which becomes a casualty to injudicious administration of the sulphones will arouse universal hostility to the " White man's medicine " and his methods. Our successes are forgotten, or ignored, it is our failures which influence public opinion. Not until the people have complete trust in us will they voluntarily practice house segregation, bring child contacts

for regular examination, attend surveys, and report for follow up checks after discharge. To establish such a degree of trust will take years of patient work in intimate contact with the people and their chiefs. For these reasons, it is considered inadvisable to follow the example of the Nigerian system of mass treatment (Garrett, 1951) which could be applied in Uganda only at the expense of neglecting the fundamental principles of preventive medicine. To summarise the practical differences:—

i. There is no ostracism of the patient with leprosy in Uganda, as in Nigeria. There is therefore no social stigma compelling him to seek early treatment or to segregate himself, if necessary.

ii. The people are less capable of taking the degree of responsibility necessary to ensure that illicit treatment and a black market in sulphones do not result.

iii. The general preventive measures, particularly public health education, require much closer supervision by a European-led trained staff.

iv. The communities are not organised in villages but live in scattered homesteads, so that the Segregation Village, so essential to the mass treatment scheme in Nigeria is not practicable. (Davey, 1940.)

The present situation.

Surveys indicate that in the area served by the Kumi sanatoria there are probably 40,000 cases of leprosy, 10% of which are lepromatous (Ross Innes, 1948). In the immediate vicinity of Kumi a number of intensive surveys have been carried out in small groups of the population and the results indicate an incidence of 47.5 per 1000. (Wheate, 1951.)

In the Mount Elgon area leprosy is rife in the densely populated fertile valleys.

In the North, a Nilotic tribal area, the incidence of leprosy is believed to be rapidly increasing, though statistical proof of this is lacking. We have, however, seen that lepromatous leprosy in Nilotics tends to be of a particularly virulent type, possibly due to a relatively low racial immunity; in addition there is evidence that some communities have a very high incidence—for example, in one school 135 children were examined and 33 were found to have early lesions, nearly all single minor tuberculoids. Similar school surveys in the West Nile District, another Nilotic area, have given the same results. (Hennessey, 1950.)

Three Methods of Rural Leprosy Control.

1. A MASS TREATMENT AND PREVENTIVE SERVICE WITHIN A RADIUS OF 20 TO 30 MILES OF THE LEPROSY INSTITUTION.

This scheme envisages a ring of five dispensaries, each situated 15 to 20 miles from Kumi, and each visited weekly by one member of the European staff and a team of African leprosy dressers. Each member of the European staff will then visit these by rota, so that particular duties, as well as those of general supervision, can be undertaken; the doctor will carry out routine examinations of patients at each dispensary every 6 weeks, the BELRA layworkers will organise surveys, follow up absentees and act as a liaison with the local chiefs at similar intervals. To operate to its fullest extent the scheme requires a permanent resident European staff of five, and its own motor transport.

Buildings will be constructed of the usual local materials by the people themselves, conveniently near to a Chief's Court. The Chief will then be able to assume responsibility for its maintenance and good order, and the official recognition of the scheme will be publicly demonstrated.

Mass Treatment will be given by the sulphones. In general, the choice of sulphone lies between DDS orally and aqueous sulphetrone by injection (Cochrane, 1951) and depends, not only on the tolerance of these particular people to DDS, but also on such factors as the popular reaction to tablets versus injections, ease of administration, cost, risks of abuse of tablets, etc. In this particular scheme, with close European supervision, DDS orally is elected, the dosage regimen being 100 to 600 mgms once weekly with due reduction after absences.

Cost is being met by the African Local Government by an annual grant, provisionally agreed at £500 per annum. This includes the running costs of motor transport.

Numbers treated will average 200 at each dispensary, as a minimum. This means that the per capita cost is 10 shillings per annum for 1000 patients, excluding the cost of the drugs. In addition out patient treatment will be available at the sanatoria.

Policy. As far as vacancies permit all children will be admitted to the Children's Sanatorium at Kumi and all lepromatous adults to the Ongino Sanatorium. Earlier diagnosis is the certain outcome of the African's willingness to attend a dispensary long before he is prepared to risk domestic instability from seeking admission to an institution. Distances between centres of treatment are such that no case of active leprosy in the area covered cannot attend. This

scheme is therefore the most practicable means of demonstrating that leprosy can be controlled and so of encouraging a sane and realistic attitude to the public health problem it now presents to the country.

2. THE RURAL PREVENTIVE UNIT.

This is planned to cover a tribal area remote from the existing leprosy institution, which will share responsibility for its organisation with the Government Medical Service in that District. It will be financed entirely by local African funds.

The scheme comprises:—

1. A staff of one European in charge of a number of African leprosy dressers and nurses, clerk, driver, etc.
2. A Central Unit, consisting of dispensary, office, stores and ward for the treatment of patients requiring temporary hospitalisation. This ward is a useful adjunct to the Government Hospital where there are objections to the treatment of leprosy patients in the general wards.
3. Five dispensaries to be visited weekly by the European in charge and a travelling team, fulfilling the same functions of providing mass treatment by sulphones and undertaking general preventive measures as outlined above.

Administration. Close liaison between the Government Medical Authorities and the leprologist at Kumi is essential. The transfer of cases requiring admission to the sanatorium, and, conversely, those no longer needing residential treatment, must be smoothly arranged.

The Central Unit is so planned and situated as to be capable of development into a small leprosarium if future needs so require.

Cost.

1. Capital Expenditure on permanent buildings (the Central Unit, houses for European and African Staff) will amount to at least £10,000. Motor transport must also be provided.
2. Recurrent Expenditure, including the salaries of both European and African staff, drugs and medical equipment, running costs and depreciation of the motor vehicle will be about £3,600. On a basis, as in Scheme 1, of 200 patients per treatment centre, this represents £3 per capita. It is, however, obvious that the scheme is elastic and can cater for many more than 200 patients per dispensary, with the additional cost only of the drugs given and perhaps the salary of one African dresser per 500 additional patients.

3. THE "SATELLITE SETTLEMENT."

This is a modification to meet particular local needs of the Nigerian Segregation Village and is being operated in a Nilotic tribal district, 200 miles from Kumi. This tribe has recently passed Local Government legislation requiring the house isolation of every case of leprosy certified by a Medical Officer to be infectious. The strong clan loyalty and absence of social stigma attaching to leprosy among these people fortunately preclude the possibility of results all too well known in other countries practising compulsory isolation.

The patients who have to comply with this bye-law have only one means of obtaining treatment, namely the Kumi Sanatoria, 200 miles away and the demand has far exceeded the supply of available accommodation and funds. The "Satellite Settlement" is an attempt on the part of the Local African Authority to provide an additional treatment centre. Initially, it will cater for only 30 resident lepromatous cases. It will be under the direct control of the Government Medical Officer in that district, who will provide the African medical staff required. In conjunction with the Settlement, several rural Government dispensaries are treating cases of leprosy as outpatients. This scheme is still in embryo. Ultimately, it is planned that a European Leprosy Control Officer be appointed to assist the Government Medical Officer in mass treatment and preventive measures and that its African medical staff be given a thorough training in leprosy at Kumi. A Rural Preventive Unit, basically similar to that already described will then emerge, having as its centre an established small leprosarium instead of a dispensary-cum-ward, and utilising the existing Government dispensary service instead of creating its own.

It should be emphasised that such a scheme is possible only because of the great public demand for leprosy treatment centres nearer than 200 miles away. These people have been aroused to the menace of this disease in their midst; they will tolerate neither inactivity on the part of the European medical authorities nor abuses on that of their African subordinates. A looser degree of European supervision is therefore safe, but it is advisable to use aqueous sulphetrone as the mass therapeutic agent in this instance.

The cost of this scheme is shared between the Government Medical Service and the African Local Authority, the former providing African medical personnel and drugs, the latter building the Settlement and meeting its maintenance costs.

SUMMARY

Three methods of rural leprosy control, based on a leprosy

sanatorium, are described. Each is organised to meet the varying needs and conditions of different parts of Uganda. The common factors between them and the principles upon which they are planned are:—

1. Mass treatment, to be effective, must be accompanied by general preventive measures.
2. Provision for the isolation of the infective case, the most important of these preventive measures.
3. Full time European supervision is essential in all but an embryo scheme.
4. The acceptance by the African Local Authority of financial responsibility for the schemes.
5. Close co-operation between the Government Medical Service and the parent leprosy institution.

REFERENCES

GARRETT, A. S. (1951) Lep Review, **22**, 47. (July-Oct. 1951).
DAVEY, T. F. (1940) Lep. Review, 11, 123.
ROSS INNES, J. (1948) East African Med. Journal, **25**, 379.
WHEATE, H. W. (1951) Ibid. **28**, 420.
HENNESSEY (1950) Personal Communication.
COCHRANE, R. G. (1951) Lep. Review, (Editorial) **22**, 43.

BACTERIOLOGICAL EXAMINATION IN LEPROSY

(ITS TECHNIQUE AND INTERPRETATION)

K. RAMANUJAM.

(Reprinted from *Laboratory Technicians Bulletin*, Vol. II, No. 2, April, 1949.)

The normal habitat of the Mycobacterium lepræ in the human host is the skin, the nasal mucous membrane and the nerve tissue. Depending upon the type of leprosy one is dealing with, it is possible to demonstrate the causative organism of leprosy in one or other of the three situations mentioned. Briefly, the smears taken from the skin and mucous membrane of the nose show a large number of the

bacilli in cases of infective leprosy, while the scrapings taken from the sheath of the peripheral nerves (ulnars and peroneals) in neural cases very often show a few organisms. The necessity for taking these smears may be either for the purpose of confirming the diagnosis (diagnosis in the first instance being made only on clinical examination) or when one has to assess the progress made by an infective case of leprosy under treatment.

THE METHODS.

Different methods have been in use for demonstrating the presence of M. lepræ. All of these except one have gone out of vogue for various reasons. However, these methods will be mentioned in passing while the method generally adopted at present will be described in more detail:

1. *The 'snip' method:* Here a piece of the affected skin is snipped off. This tissue is then rubbed vigorously on the slide until all tissue material is transferred to the slide. The smear is fixed, stained and examined.
2. *The 'puncture' method:* The skin is pinched hard between the blades of a curved clamp so as to render that part of the skin ischæmic. The skin is then punctured with a thick hypodermic needle. The serum which exudes from the puncture holes is spread on a slide, stained and examined.
3. *The 'cutting punch' method:* This method consists of removing a piece of skin with a biopsy forceps and smearing the deeper part of the tissue on a slide. The smear is then stained and examined.
4. *The 'incision' method:*

THE TECHNIQUE OF TAKING SMEARS BY THE 'INCISION' METHOD

Since the Mycobacterium lepræ resides in the layers of the dermis, this method aims at taking the material for examination from that site. This was first outlined by Wade in 1935 and is now widely adopted.

The area to be examined is thoroughly cleansed with cotton wool and spirit and allowed to dry. The skin is pinched up between the thumb and index finger of the left hand and firm pressure applied so as to render the area less vascular. When this is not possible, apply as much pressure as possible laterally. The object of rendering the area ischæmic is to obtain as much of the tissue juice as possible, and the minimum amount of blood which would otherwise make the smear reading difficult.

With a sharp sterile scalpel a small incision is made in the skin (about 5 mm long), deep enough (about 2mm) to get into the corium. If any blood oozes from the incision it is wiped off. Now

with the knife blade turned transversely to the line of incision and still retaining the pressure on the fold of the skin with the fingers, the bottom and sides of the incision are scraped repeatedly to obtain a little tissue juice. The material so obtained on the tip of the scalpel is transferred on to a clean microscope slide and a uniform smear is made over a small area. The smear is then fixed by waving it over a flame and stained in the usual way.

There are certain precautions to be taken if one is to guard against errors that might creep in.

(i) The skin should be rubbed vigorously with alcohol, ether or denatured spirit, not only to render it aseptic but also to get rid of any acid fast saprophytes which reside on the skin surface.

(ii) It is necessary to clean the blade of the scalpel with spirit and flame it before using it for taking the next smear, even if it be in the same patient. It is possible that if these precautions are not taken, the bacilli obtained from the first smear may be transferred on to the second one and thereby vitiate the bacteriological readings.

Taking Nasal Smears

Examination of the scrapings from the nasal mucous membrane forms part of a routine bacteriological examination. The material is obtained by scraping the mucous membrane over the nasal septum well above the external nares.

A sharp pointed tenotomy knife may be used for this purpose. When this is not available a simple cheap instrument suggested by Wade may be used instead. This consists of a paper clip straightened out and one end flattened to form a small scoop. This is then mounted on a piece of wood or bamboo which serves as a handle.

In sufficiently good light the tip of the nose is pushed up with the thumb of the left hand so as to expose the nasal septum. One of these instruments is introduced into the nasal orifice high enough and the mucous membrane covering the nasal septum is scraped off. The material thus obtained is then spread over a clean glass slide so as to give a small uniform smear.

Routine Smears

Since there is no yardstick by which one can assess the progress made by infective cases of leprosy, we are completely dependent upon the results of smear examination made from time to time. The need for taking multiple skin smears including those from the nose cannot be sufficiently stressed when one realises the " treacherous " nature of the skin lesions in lepromatous leprosy. Areas of skin which appear apparently normal clinically have revealed the presence of M. lepræ. However, if this examination is done only for the purpose of confirming the diagnosis, a few

smears may suffice. But when one has to follow up the cases under treatment, multiple smears are absolutely necessary. It may be said that this practice of taking smears is an infliction on the patient.

It is our practice here to take sixteen smears from each case—one from each ear, cheek, forehead, nose, chest, back, buttock and thigh and also from the chin and arm. It is convenient and also economical to take 8 to 10 smears on each slide. In order to avoid any confusion that may arise while the smears are examined, a good practice will be first to make a list of smears to be taken on a piece of paper and then start taking the smears in that order.

Staining of Smears

CARBOL FUCHSIN SOLUTION

Boil 10 gms. of Basic Fuchsin in 100 c.c. of absolute alcohol under a reflux condenser for half an hour. Allow the solution to cool.

Dissolve 50 gms. of Phenol in 950 c.c. of distilled water. Add this to the Fuchsin solution and shake well. Keep for five days for ripening the stain. Filter the solution before use. The solution keeps indefinitely.

(B) THE STAINING TECHNIQUE*

(i) Fix the smears by waving the slide over a flame.

(ii) Flood the slide containing the smears with the 'staining' solution and leave it aside for 15—20 minutes. If there are a number of slides to be stained they may be immersed in a staining jar containing the staining solution. Wash well in running water.

(iii) Decolourise with 15% sulphuric acid for a few seconds till the smears show a faint pink colour. Wash well in running water.

(iv) Counterstain with 1% aqueous methylene blue for 3 to 4 minutes. Again wash in running water, allow it to dry, and examine under an oil immersion lens.

While examining smears it is well to bear these things in mind:

(i) When in doubt, the organism is probably not M. leprae.

(ii) At least 200 fields should be examined before a slide is passed as negative.

& (iii) No slide should be declared positive on the strength of finding a solitary bacillus.

* This method has been modified as described in the original article. —EDITOR.

While examining the smears one will encounter the organisms in various stages of disintegration. They may appear beaded, fragmented and granular, and sometimes as acid-fast dust. It will also be advantageous to make a note of the nature of the organism seen—(e.g., Rt. ear 4+ fragmented; Lt. ear 3+ granular; Rt. cheek 5+, etc.)

Conclusions

When taking material for bacteriological examination it is well to remember the following points:—

(1) Have the patient in good sunlight and take smears from the obviously affected or suspicious areas. Take as many as 16 smears as a routine from the areas mentioned earlier.

(2) Take as much of the tissue pulp and as little blood as possible so as to render the microscopic examination easy and clear.

(3) Always make it a point to flame and clean the blade of the knife between successive smears so as to avoid errors.

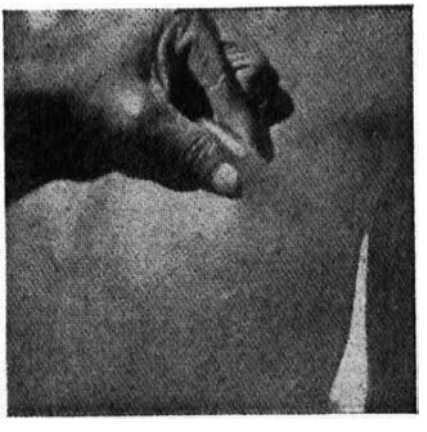
(4) When in doubt about the identity of the organism never call it M. lepræ.

I wish to acknowledge my grateful thanks to Dr. R. G. Cochrane for permitting me to write this paper and for his valuable suggestions.

References:

(1) Cochrane, R. G.—A Practical Text Book of Leprosy (1947).
(2) Muir, Ernest—Manual of Leprosy (1948).
(3) Muir, E.—Leprosy; Diagnosis, Treatment and Prevention (6th edition).

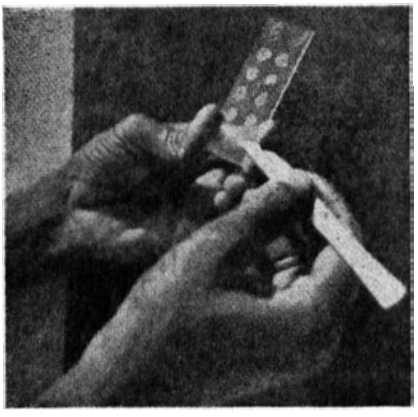
The lesion to be smeared



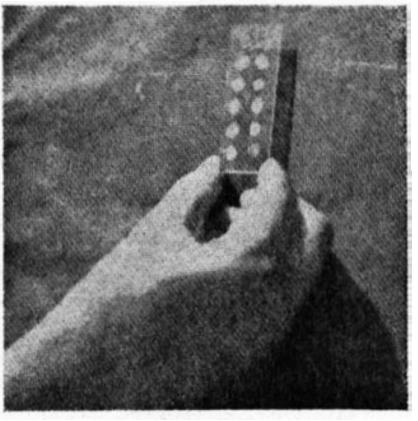
The lesion pinched up in a fold of the skin

The incision made

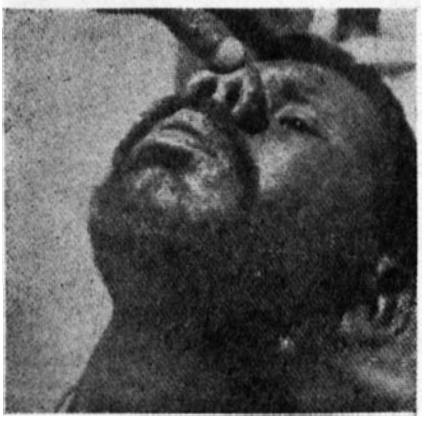
The tissue pulp scraped



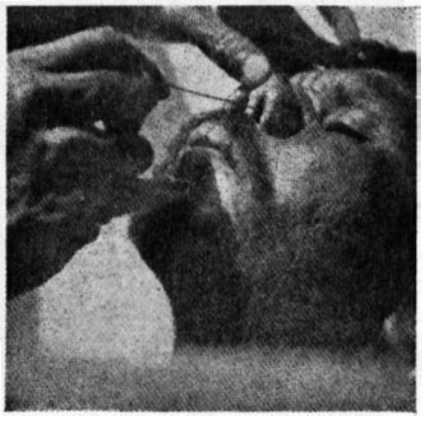
The material transferred to a clean slide so as to make a thin small smear



The slide with multiple smear ready for staining



Taking Nasal Smear
The tip of the nose is pushed up



Taking Nasal Smear
With a suitable instrument the mucous membrane over the nasal septum is scraped

A CONCENTRATION METHOD FOR ACID FAST BACILLI IN SKIN BIOPSIES FROM LEPROSY PATIENTS

V. R. KHANOLKAR

(Reprinted from "Memorandum on the Treatment of Leprosy with Sulphones." Indian Council of Medical Research, Special Report Series No. 24, 1952)

A skin biopsy of approximately 5 x 3 x 5mm. is obtained from a selected area in persons suspected to be suffering from leprosy. The tissue is immediately dropped in about 3 c.c. of one per cent acetic acid and left there between four to eight hours. It is then taken on a clean dry glass slide and the epidermis is easily scraped off from the dermis, by means of a sterile scalpel.

The tissue, now free from epidermis is dropped into a pyrex glass homogeniser tube (Fig. 2), with an inner ground glass surface, in fresh 3 c.c. of one per cent acetic acid and crushed at about 2,000 r.p.m. with an electrically operated mechanical glass crusher (Fig. 1) for about five to ten minutes. The crushing process is con-

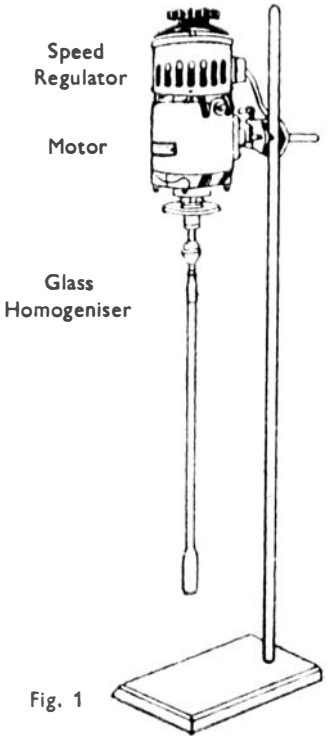


Fig. 1

Pyrex tube with ground inner surface

Fig. 2

Platinum Loop

tinued until a homogenous milky emulsion of the tissue particles is obtained while a residual cake of the tough dermal tissue sinks to the bottom of the tube. The tissue particles adhering to the sides of the stirrer and the tube are washed down with about one to two c.c. of one per cent acetic acid, bringing the contents to a total volume of about 5 c.c.

Twenty drops of petroleum ether sulphuric ether mixture (1:10) are added to the turbid fluid with a drop bottle. The tube is shaken vigorously to ensure thorough mixing, corked and allowed to stand in a test tube rack for about 15 to 20 minutes.

10 c.c. of distilled water is let into the tube, along its side, washing down any particle adhering to the wall of the tube. From the white or amber coloured ring formed on the surface after two to five minutes, eight drops are carefully picked up with a sterile 3 m.m. platinum loop and deposited on a clean glass slide. The next eight drops are placed on another clean slide. The drops are then spread over an area roughly 2 x 2 cms. The slides are kept in a covered Petri dish and are allowed to dry in an incubator at 37°C.

The dried smears are fixed by flooding the slides with Carnoy's fixative which is poured off after 15 minutes and the smears dried in air. These dried smears are stained by a slightly modified Ziehl-Neelsen method. Instead of warming the Fuchsin stain on the slide, a test tube containing the Carbol Fuchsin solution is warmed in boiling water in a water bath and poured through a filter paper on the slide. The stain is kept on the slide for ten minutes. The decolourisation is then carried out with 33 per cent Hydrochloric acid for 20 to 30 seconds and the slide, carefully washed in a Coplin jar with running water for at least five minutes. A very dilute solution of Azur II is used as a counter stain. The smears are allowed to dry completely by leaving the slides in such a manner as to prevent the accumulation of dust on the smear surface.

The entire surface of the stained and dried smear is carefully examined for acid fast bacilli under an oil immersion objective.

Carnoy's Fixative (E. V. Cowdry—Laboratory Technique in Biology and Medicine).

†Absolute Alcohol	6 parts
Chloroform	3 parts
Glacial Acetic Acid	1 part

†Rectified spirit (not methylated spirit) can be used instead of Absolute Alcohol.

BACTERIOLOGICAL INDEX IN LEPROSY

R. G. COCHRANE

Since the introduction of sulphone therapy several workers (Muir, Dharmendra, Cochrane) have realised the necessity for a method of assessing the degree of positivity in leprosy. Wade some years ago suggested the possibility of calculating a bacteriological index, but as far as is known this was not generally adopted. At the beginning of the therapeutic trials on the new sulphone drugs in leprosy, the author discussed with Dr. C. G. Pandit, the then Director of the King Institute, Guindy, Madras, the possibility of working out a bacteriologic index which could ultimately be used for statistical purposes. As a result of suggestions from Dr. Pandit and Dr. Ramanujam the following method was finally chosen:—

Sixteen smears are taken by Wade's slit method and graded from 6+ to negative. Smears are graded as follows: 6+, bacilli and many globi in every field examined; 5+, bacilli and few globi in every field examined; 4+, bacilli but no globi in every field examined; 3+, bacilli in 10 per cent or more fields examined; 2+, bacilli in 4 per cent or more of fields examined. 1+, bacilli in 2 per cent or more of fields examined. When the result is less than 1+ then Muir's method is adopted, the numerator being the number of bacilli and the denominator the number of fields examined, e.g. if in 100 fields five bacilli were counted, the result would be 5/100. with sulphone therapy the bacilli break up into granules and are not easily counted, so if there were five groups of granules in 100 fields the result would be 5/100 (granular). Half a point is recorded if the index is under one. The total number of readings are added up and divided by 16 and this gives a number which is taken to the nearest digit. The resultant figure is termed the "bacteriologic index." For instance, if an examination showed the following smear results:—

4	smears 6+	(4 × 6 = 24)	24
2	,, 4+	(2 × 4 = 8)	8
5	,, 3+	(5 × 3 = 15)	15
5	,, 2+	(5 × 2 = 10)	10
		Total	57

the bacteriologic index would be 57 divided by 16, which is 3.56—or, to the nearest digit, 4. When the index drops below 0.5, then it is recorded as >0.5. Our criteria are as strict as possible. For

instance, if only a few acid fast granules are found in one area of the 16 smears, the result is still recorded as >0.5. Naturally, therefore, in reporting results, the method of assessing the bacteriologic state of the patient must be noted, for if a few acid fast granules are considered of no importance and the patient in consequence is placed in the negative group, the negative rate will rise considerably. We, however, consider that the presence of bacilli, whether as granules, beaded forms or acid fast dust, are of importance and include such cases among our positive findings.

Other workers who have suggested a bacteriological index have used a less number of smears. Muir chose five and Dharmendra six. Muir's method is described as follows:—

" At each examination five smears were made from the skin at places where experience indicated the most bacilli were likely to be found, cutaneous and subcutaneous nodules being chosen when present. Each smear when found positive was counted in one of four grades with one, two, three or four points respectively: one point indicating a few bacilli, four point a massive infection, and two and three points intermediate grades. The total of points at an examination is known as the " Bacteriological Index " or B.I., the maximum being 20 for the five smears."

Dharmendra adopts a similar method to that devised at Chingleput, but his method of estimating the number of bacilli is somewhat different, and he indicates the degree of positivity as slight, moderate, heavy and massive or in grades of +1, +2, +3, +4, as under:—

" Slight " or + (1+)	Bacilli not found in every field but only in an occasional field, and there are not more than two or three bacilli in a field perhaps with one or two small globi in 50 fields.
" Moderate " or ++ (2+)	Bacilli found in every field, but not more than about ten in each field with a few globi here and there.
" Heavy " or +++ (3+)	Numerous bacilli and globi found in every field.
" Massive " or ++++ (4+)	Innumerable bacilli and large number of globi found in every field.

If a number of smears are examined and the degree of positivity varies, an average degree of positivity could be expressed in the form of a " bacteriological index " by adding the degrees of positivities of all the smears and dividing the total by the number of smears examined. For example, six smears taken from a case may give the following results:—

Smear No. 1.	Right ear	4+
Smear No. 2.	Left cheek	3+
Smear No. 3.	Chin	4+
Smear No. 4.	Right forearm	2+
Smear No. 5.	Left thigh	2+
Smear No. 6.	Nose	3+
	All six smears ...	18

The index can be obtained by dividing 18 by 6, i.e. the bacteriological index will be $18/6 = 3$."

The chief objection to the index adopted for the Therapeutic Research Unit at Chingleput is that sixteen smears is too great a number to take from one individual, and time consuming and tedious. For ordinary purposes Dharmendra's method is one which can be recommended. Where detailed research in therapeutic remedies and careful assessment of results are necessary it seems logical that the greater the number of smears taken, and the higher the grading of the positivity of the slides, with the examination of at least 100 fields, makes for more accurate appraisal of the results. Where a large number of patients are on therapeutic test the number of examinations is considerable, and therefore the routine smears have to be done by a technician. To be able to choose areas likely to be positive needs much experience and careful examination in a good light. Therefore our practice at Chingleput was to allow the technicians to smear all cases, and a careful check-up by the doctor in charge of research was undertaken every six months, when every patient was meticulously examined. By taking sixteen smears and grading the positivity of these from negative to six plus, we felt we reduced the margin of error to such an extent that our findings could be statistically analysed. It is hoped that in a future number of *Leprosy Review* an article will be published on " Principles of Clinical and Therapeutic Experiments in Leprosy, with particular reference to Sulphone Therapy." In this article will be included a statistical analysis of our findings, the statistical work having been done by a trained statistician.

This present article is written in order that workers may be aware of the different methods of assessing the bacteriological index, and to give them the opportunity to choose the method most suitable to their particular needs. The merits of these various methods cannot be assessed until statistical comparisons have been done. For work in therapeutic trials in leprosy, the greater the accuracy in estimating the progress towards a state of negativity the more sure

will be the results, and thus one can guard against impressions and wishful thinking, all too common in leprosy, and which are liable to vitiate the final conclusions.

MEMORANDUM SETTING OUT THE BRITISH EMPIRE LEPROSY RELIEF ASSOCIATION'S RESEARCH PROJECT IN EAST AFRICA*

by

R. G. COCHRANE.

The advances in the therapy of leprosy have opened up the way towards a better understanding of the disease. Now that it has been demonstrated that leprosy is amenable to treatment interest has been created in the search for more efficient, more rapid, and more certain remedies for the " cure " of a disease which has baffled the Medical Profession for decades, if not centuries.

The advances in Chemotherapy place at the disposal of the Medical Profession new and powerful drugs, but if we are to avail ourselves of the opportunity the new age of chemotherapy has placed in our hands, an essential pre-requisite is a better understanding of the disease.

There are research stations in Britain and the Empire for Tuberculosis, for Malaria, for Trypanosomiasis, and many other conditions, but, despite the fact that of the estimated five to ten million victims of leprosy more than half are probably citizens of the Empire and Commonwealth, there is no comprehensive research and training centre.

There are centres which undertake research—e.g. Calcutta, Uzuakoli, Sungei Buloh—but these are either limited in their scope or activities. For example, Calcutta is handicapped by having no adequate In-patients institution; Uzuakoli is chiefly a therapeutic unit and has few or no facilities for clinical photography and histo-

* This Memorandum was accepted by the Medical Committee of the British Empire Leprosy Relief Association at their meeting on 25th July, 1952. The Committee issued a directive that research in Epidemiology, Immunology and Therapy should first be undertaken, leaving other aspects of the programme for later consideration.

pathology. Sungei Buloh is in an area of political uncertainty, and, therefore, personnel problems arisè.

FUNCTIONS OF THE BRITISH EMPIRE LEPROSY RELIEF ASSOCIATION

Apart from informing the general public of the need for leprosy relief, the British Empire Leprosy Relief Association's main function is to advise Governments and other bodies as to the most efficient way of bringing leprosy under control in the Empire and Commonwealth. If this is to be done adequately, and if the Association's opinions are to be of value, and not second-hand, a Research Station is an absolute necessity. It is quite true that research in leprosy must never be conducted in a water-tight compartment, but the research worker must be in touch with scientists in allied fields, and, therefore, a research station should be within reasonable reach of Medical Research Institutions. Because one of B.E.L.R.A.'s functions is to stimulate pioneer and pilot experiments in leprosy, it is vital that this organisation, in co-operation with the Colonial Governments, should contemplate establishing a Research Unit. The objectives of this Research Unit should be—

I. Research in all practical aspects of leprosy, with a view to
   (1) Acquiring a better understanding of the disease.
   (2) Assessing critically new Chemotherapeutic remedies.
   (3) Investigating speedier and more effective methods of control.
   (4) Studying ways and means of preventing and alleviating deformities.

II. The establishment of a Central Training Institution where workers would receive a comprehensive training in leprosy.

I. RESEARCH IN ALL PRACTICAL ASPECTS OF LEPROSY.

(1) I stress the point " practical aspects " because while basic research is essential it must have a practical objective and lead to a better understanding of the disease, and not just result in information of academic and theoretical interest. Nevertheless, an adequate appreciation of the time needed for fundamental research must be present, and the research worker must not be expected to produce results of significant practical importance every year; neither must his work be solely judged on this criterion. A better understanding of leprosy will ultimately influence the practical policies of treatment and control, but years of research may be necessary before its practical application can be appreciated. In discussing research work in these terms I shall consider the following subjects, which need special attention.

a. Epidemiology.
b. Histopathology.
c. Bacteriology.
d. Immunology.
e. Animal Inoculation.

a. EPIDEMIOLOGY.

While much epidemiological research is highly technical and only of practical application over a very prolonged period, nevertheless it is quite true to say that we know little or nothing about the factors which cause leprosy to increase under natural conditions. Detailed epidemiological investigations apart from a limited area in the Philippines, in Brazil, and in certain parts of India and Nigeria, have received very little attention, particularly on a long term basis. It may not be correct, for instance, to state that solely because sulphone therapy has been given on a wide scale, leprosy has been controlled within certain areas. Nevertheless it may be said that leprosy control has been greatly assisted through the discovery of the sulphones, and has given confidence to workers in discharging patients. To investigate all the factors of decline or increase of leprosy, and to be able to judge the stage of the epidemic in any given area, would be of utmost practical importance, and would save unnecessary expenditure in areas where all the evidence available indicated that leprosy was on the decline.

b. HISTOPATHOLOGY.

While it may be said that the study of the detailed histopathological process in leprosy is an item of basic research more of academic than practical importance, nevertheless, if we are to understand the factors which influence the healing of the disease, either spontaneously or by means of chemotherapeutic agents, the more knowledge we have of the reactions of the dermal tissues—favourable or unfavourable—to invasion by the *M. leprae*, the greater will be our understanding of the processes necessary in chemotherapy, and the better will we be able critically to assess therapeutic results. Further, the recent suggestive work of the Bombay workers indicates that the answer to the development of leprosy may be found in the skin, and it appears that the *M. leprae* invade the nerve plexuses of the skin first, and spread from these structures. This work, and the investigation of the presence of bacilli in the dermis of contacts of open cases is of great importance, but to confirm these observations needs patient, meticulous, and prolonged study of a large number of smears and sections from contacts.

As a result of the more detailed study of histopathology the classification of leprosy is being better understood. Classification

of disease can hardly be considered of academic importance only, for without a proper appreciation of this, it is difficult to explain the various clinical and immunological anomalies which are seen in leprosy. The complete elucidation of the protean clinical manifestations of leprosy will only be achieved by a detailed long-term study of the histopathology of the skin in leprosy.

I believe that therapy should be combined with the study of skin changes during resolution of the disease under treatment. If this were done more, and compared with resolution or extension of the disease in untreated cases, fewer premature claims for success would be made, and a more accurate assessment of the benefits of therapy would be available. The question of relapses, and the nature and viability of the granular forms of the *M. leprae*, entails not only detailed histological studies, but observation over a number of years.

While certain histopathological techniques—e.g. the study of nerve changes, the exact position of the *M. leprae* within the nerve, the nature and mode of spread along the nerve—*need special methods and knowledge*, a research station with good clinical records can always enlist the help of specialist workers and send material to these workers for their comment and *guidance in future research*. Only detailed methods of histopathological research will answer a number of problems which have arisen in the new and successful therapy of leprosy with the sulphone group of drugs.

c. BACTERIOLOGY.

I am aware that research in the bacteriology of leprosy is not only extremely difficult, but, up to now, has been extraordinarily barren of results. Nevertheless recent work, indicating the importance of nerve tissue in the evolution and development and spread of leprosy, opens up new lines of research, and a fresh approach to cultivation in vitro of *M. leprae* and animal inoculation. Advances in chemotherapy of leprosy are very seriously handicapped because of the lack of success in culturing *M. leprae*, and the failure to infect animals with leprosy. If these disadvantages could be overcome, a more detailed study of the metabolism of *M. leprae*, could be undertaken, and our trial of drugs might be less confined to those which have been shown to be effective in tuberculosis. Admittedly this may require complicated and costly apparatus, but, now there are possibilities of despatching material by the freeze-dry technique, lines of development in the culture of the *M. leprae*, which are suggested by the research on other aspects of the disease, could be followed up by sending the material to well-equipped laboratories in this country. No part of East Africa is

more than 24 hours by air from Great Britain, and by the new Comet service Entebbe in East Africa is but twelve hours from London.

d. IMMUNOLOGY.

The detailed immunological study of leprosy is again a long-term project. The work of the South American and French workers in B.C.G. vaccination and the lepromin test is most interesting, and should be followed up on a long-term basis. There seems to be considerable evidence that in children, and possibly also in adults, a lepromin negative reaction is converted into a positive after B.C.G. vaccination. The importance of this in child contacts is obvious, but finally to assess (a) whether this reaction is actually accompanied by increased resistance to *M. leprae*, and (b) whether any tissue immunity which may be established is permanent, needs detailed and careful observation of persons in an endemic area for many years. To clear up these and cognate questions epidemiological investigation will be necessary in an easily accessible area where leprosy is highly endemic. The research unit contemplated in E. Africa would be a most suitable centre from which to carry out a long-term research project of this nature.

e. ANIMAL INOCULATION.

One of the greatest handicaps to a better understanding of the life history of *M. leprae* is the lack of a suitable experimental animal. With the lead which recent work has given on the importance of the nerves in leprosy, and the work on cortisone and ACTH on inhibiting healing processes, an entirely new avenue of animal experimentation has opened up. A research station in East Africa, where large animals—e.g. monkeys—are more readily available, might contribute significantly to our knowledge in this respect.

In this connection, it may be said that an endeavour is being made to secure the help of research workers in this country. This would be of great value to such a research station as is contemplated, because workers in a research station in East Africa could be kept in constant touch with experienced research workers in the ancillary fields of bacteriology, including experimental pathology.

(2) CRITICAL ASSESSMENT OF NEW CHEMOTHERAPEUTIC REMEDIES.

The first requirement in assessing chemotherapeutic remedies is a knowledge of how they act on the *M. leprae.* Therefore, if we are to have a clear understanding of the way chemotherapeutic remedies and antibiotics act in leprosy, such phenomena as the following need fuller elucidation, (a) erythema nodosum, (b) changes in the morphology of *M. leprae,* (c) reservoirs, e.g. nerves,

which may continue to harbour *M. leprae*, and from which they may spread and cause relapse. This aspect of research would, therefore, be an important item in the research programme of such an institution as is envisaged by B.E.L.R.A.

Because of the increasing number of chemotherapeutic and antibiotic drugs being advocated against mycobacterial disease, it is essential to have a fully equipped research unit. I am of opinion that much money would be saved and unnecessary suffering, through the creation of exaggerated hopes, would be avoided, if all new drugs could first be tried in such a station. Admittedly, there are several institutions in which therapeutic trials can be undertaken, but there are special advantages when they take place in a centre where there are facilities for controlled comparisons, histopathological examinations, and the keeping of photographic and other records.

Initial chemotherapeutic trials could also be advantageously undertaken, for these can be combined with detailed biochemical estimations. In this way much information could be collated as to the method of the action of drugs on *M. leprae*, and their actual or potential toxic properties.

(3) INVESTIGATION OF SPEEDIER AND MORE EFFECTIVE METHODS OF CONTROL.

The place of treatment, particularly sulphone therapy, in the control of leprosy, is a subject which demands close investigation. As already stated, there are so many factors influencing the stage of the " epidemic " of leprosy, not only in a given country, but in a particular area of the same country, that only the most general conclusions can be reached as to the effect of a given therapeutic remedy on the control of the disease. Therefore, it would be of utmost value to plan a long-term experiment in a suitable area, with adequate controls, on the influence of effective anti-leprosy drugs on the spread and control of leprosy. Such a project would involve preliminary detailed survey, and periodic resurveys. Statements on the control of leprosy by means of therapy are sometimes made on insufficient data.

(4) STUDY OF WAYS AND MEANS OF PREVENTING AND ALLEVIATING DEFORMITIES.

One of the most serious problems in leprosy is the question of deformity which is such a frequent end result of the disease. It is true that the more widespread the use of sulphones, the less likely are the unfortunate sequelae of leprosy to be seen. Nevertheless, as the problem of deformity due to paralysis and paresis of muscles is likely to continue to be serious for many years, investigation

into the methods of preventing or alleviating these conditions deserves high priority in our planning. Admittedly, if one is contemplating orthopaedic and physiotherapeutic measures, an institution in which there is already a general research unit would be ideal for this purpose, and, therefore, in all planning the claims for orthopaedic and physiotherapeutic investigation should be considered.

II. A CENTRAL TRAINING INSTITUTION.

A thorough training in leprosy is as essential as teaching in tuberculosis. It is a great handicap for young doctors, who become initially interested in leprosy, not to be given facilities to acquire a basic knowledge of this speciality before assuming responsibility for an institution, and, as is frequently the case, also for leprosy prevention in the area around the leprosy colony.

Outside Calcutta there are no set courses of leprosy instruction. If a young medical man is not only to offer for leprosy, but to remain in this work, it is essential that he be given a training for at least three months. Recruits, particularly medical men, for leprosy work are lamentably few, and I believe this is largely due to the fact that there is little opportunity given to young men to appreciate the fact that leprosy is a most interesting speciality, and one which gives ample scope for their talents.

ORGANISATION OF UNIT.

It is proposed to place this unit under the charge of an experienced Leprologist, Dr. Ross Innes, who would have under him:—

(1) A fully trained laboratory technician.
(2) A biochemist.
(3) A secretary (clerical) to the unit.
(4) Junior clerks and junior technicians.

In so far as the Member Governments of the East Africa High Commission would be associated with B.E.L.R.A., reports of the working of the unit would be sent not only to the Secretary of the Medical Committee of B.E.L.R.A., but also to the Colonial Office and to the Director of Medical Services in the three Territories. This would be of inestimable value to the work, and would relate leprosy to other research projects already in existence in East Africa.

COST OF UNIT.

Detailed plans remain to be worked out when the site is chosen and general principles of organisation have been drafted. It is, however, estimated that the capital cost would be in the neighbourhood of £30,000 and the recurrent cost £8,000. B.E.L.R.A. could

see its way to providing £8,000 to £10,000 for the capital cost, leaving some £20,000 to £22,000 to be raised. The recurrent cost would, we hope, be met by B.E.L.R.A. in co-operation with the East Africa High Commission and its constituent Governments.

The question of future recruitment of other Senior Staff may be raised, as the Leprosy Research Worker contemplated is a very senior Officer. I am of opinion, and I have reason for this statement, that once this research station is under way, it would not be difficult to secure a keen but younger person to assist Dr. Ross Innes.

Leprosy has entered the field of practical medicine, and the stage is now set, not only to correlate and investigate the importance of certain relatively simple facts*—e.g. the part diet plays in influencing the development and spread of leprosy in a given area, the importance of tribal and other customs, etc.—but to undertake detailed research into the pathology, treatment and control of leprosy. Not only should our increasing knowledge of chemotherapeutic agencies be used to combat this disease, but, in addition, as a result of a better understanding of the disease, suffering, particularly that due to deformities and paralysis, should be prevented, and leprosy at last cease to be the terror it is in many of Her Majesty's Dominions and the Commonwealth at large.

ROBERT G. COCHRANE,
Medical Secretary.

May, 1952.

ACKNOWLEDGMENTS.

I am grateful for the help and advice of Dr. James Ross Innes, Interterritorial Leprologist to the East African High Commission, in the preparation of this Memorandum.

* In this connection attention should be drawn to the Report of the late Professor McSwiney on the importance of relatively simple observations and facts and their bearing on disease in East African Medical Research, 1935-36.

REVIEWS

Indian Council Medical Research. Special Report Series, No. 19 (1951).

"Studies in the Histology of Early Lesions in Leprosy" by V. R. Khanolkar. This monograph focuses attention on the need for the basic study of early lesions in leprosy. Some, on reading this contribution, will exclaim in the words of Anatole France quoted by the author. "There are some that will say that . . . this is not the true doctrine. There are others who will say I have said nothing more than what everyone already knows." This quotation is a

mirror into the mind of a patient worker, who, viewing the history of a subject, gathers up from the past and adds his own carefully documented research work, and produces a contribution of outstanding merit.

In a short monograph profusely and beautifully illustrated, Dr. Khanolkar sets forth to show that there is good evidence to indicate that the entrance of M.leprae into the body is through the skin, and that the organism has a predilection for subcutaneous nerve tissue, particularly in the early stages of life when there is a continuous process of degeneration and regeneration, and when the areas of skin are subjected to minute injury and friction. Leprosy is neural in its inception and the M.leprae first appear in clinical lesions in the small nerve plexuses in the skin and travel up the finest nerve twigs in an ascending infection.

It is impossible to give an adequate summary of this work, and those interested are strongly advised to read the whole article. This carefully reasoned out hypothesis, which Dr. Khanolkar has set forth, is substantiated by patient and meticulous study of sections from early lesions. The silent phase of the disease—that is before actual clinical symptoms manifest themselves—is lucidly explained and illustrated by beautiful drawings. The reason why certain lesions become tuberculoid and others leproma is logically set forth, and indicates that a classification of leprosy is not only possible, but this must—as in the Havana and South American classifications —be based on the study of the immunology of the disease, and due stress is placed on the lepromin test. As has been suspected by certain workers, Khanolkar shows that leprosy starts as a local invasion of the skin, and that its development in the body depends on (a) the bacilli being able to burst out from the subcutaneous nerves and nerve plexuses of the skin, and, (b) on the ability or inability of the tissues to respond to the presence of the M.leprae by a vigorous reaction. The argument is built up powerfully and logically and explains the reasons for the clinical types of leprosy.

In this study the evidence that the bacilli can remain in the granular form in the nerves causes one to be cautious lest sulphone therapy is discontinued too soon and patients undergo unnecessary relapses.

This monograph has crystalised our knowledge of early histopathological conditions in the skin, and is a landmark in leprosy research. Dr. V. R. Khanolkar deserves congratulations on the painstaking manner in which he has collected data and on the excellence of his technique. This contribution marks a step in the advance and understanding of leprosy as important as any during the last two or three decades. R.G.C.

LEPROSY REVIEW. VOLUME XXIII.

INDEX TO VOLUME XXIII (1952)

O.

P.

R.

S.

U.

Z.