LEPROSY REVIEW

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VOL. XVIII, NOS. 2 AND 3 APRIL-JULY 1947

CONTENTS.

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EDITORIAL.

The fuel crisis in Britain early this year held up the publication of the January number of the *Leprosy Review* until late in April. The April and July issues of the Journal are therefore combined in the present number.

Readers will learn with regret that Dr. E. Muir has resigned from the combined post of Editor of this Journal and Medical Secretary of the B.E.L.R.A. He has, however, consented to act with Sir Leonard Rogers as Honorary Medical Adviser to the Association.

Dr. Muir became editor of the *Leprosy Review* and Medical Secretary of B.E.L.R.A, in 1935.

The *Leprosy Review* of October 1935 states, " It will be noted by our readers that Dr. E. Muir, of the Calcutta School of Tropical Medicine, is taking over the Medical Secretaryship of the Association from October 1st. Dr. Muir will edit the new volume of the Review from January 1936 . . . . We are convinced that under Dr. Muir's editorship the *Review* will become increasingly useful and valuable to those who wish to keep in touch with modern advances and have not the time to read the more technical journals." This prediction has been amply fulfilled.

From the same issue we quote an appreciation of Dr. Muir on the occasion of his retirement from the post of leprosy research worker at the Calcutta School of Tropical Medicine. " His width of view, insight and patient work have resulted in far reaching advances which have been of incalculable value in placing the dreaded leprosy within the pale of preventable and curable diseases, using the latter word in its popular sense. The use of creosoted pure hydnocarpus oil and ethyl esters prepared by his simple method have furnished effective treatments at a cost within the reach of all. The importance of the stress he has laid on the treatment of all complicating debilitating diseases to increase the resisting power of the patients is universally recognised. The surveys he organised throughout India have revealed the nature and extent of the leprosy problem and enabled hundreds of leprosy clinics to be opened and treat some 100,000 cases a year, mostly in an early stage, at a minimum cost; and this in turn has led to the recent development of following up the patients to their houses and arranging for the home isolation of the infective cases in order to strike at the root of the problem by stopping new infection. Dr. Muir has completed over 30 years' service in Palestine and India,

where he laboured as one of the most successful and hard working of medical missionaries up to 1920. Our Association is very fortunate in being able to make use of his unrivalled experience in the cause that he has so much at heart."

No truer index than this tribute could be given of the value of Dr. Muir's services to the British Empire Leprosy Relief Association and the cause of leprosy work in general.

We commend to our readers a close study of Professor Araujo's modification of the clamp method for smear taking. The standard slit and clip methods of taking smears are essentially teased tissue preparations where bacillary pockets may be overlayed or overlooked. These methods can only be regarded as sample "spot surveys" of bacillary incidence. The clamp method, if it is found widely successful, may by its relative exclusion of tissue debris, prove the basis of a new technique for bacillary counts. Closely linked with this is the modification in staining method suggested by Dr. Oliveira Castro as a development of Cooper's technique. The method would appear to bring us a new precision in the study of the morphology of the bacillus. This work opens up the way for considerable further investigation. The part played by these bacillary nodules in the physiology of the bacillus is by no means clear and further research is needed on the incidence of these nodules in the different phases of leprosy and in lepromatous and tuberculoid reactions. Slides of the clamp method and of the new staining modification can be made by any worker with accurate technique and with the essential equipment of a simple laboratory.

One of the functions of the British Empire Leprosy Relief Association is to make known the results of such research and to stimulate wider application and study of such new methods, so that information gleaned from places with widely varying leprosy conditions can be pooled and assessed. It is to be hoped, therefore, that wherever laboratory facilities are available the clamp method and Dr. Oliveira Castro's staining modification will be studied with a view to obtaining composite experience. Only thus can we obtain advances in technique which can be recommended for general acceptance.

Readers will welcome Dr. Cochrane's article on child leprosy—a subject on which he speaks with authority and which cannot be overstressed. It is unfortunately still true that adult leprosy per se receives in many endemic countries a disproportionate share of the available effort in the campaign against the disease. It is still insufficiently realised that the main importance of an adult infective leper from the public health point of view is the number of children

within contact range of that leper. It is also unfortunately true that in many places the conscience and imagination of the community have, as yet, been insufficiently aroused to the essential tragedy of this needless inoculation of children.

In this issue, by the courtesy of Dr. Lowe, we reprint an article, "Comments on the History of Leprosy" from *Leprosy in India*, January 1943. We feel that this historical study merits the careful attention of those who may have missed it through the restrictions of its original wartime publication.

In conclusion we present the following message to our readers from Dr. Ernest Muir:—

In retiring from the Editorship of *Leprosy Review* I am glad to be able to hand over the task to Dr. Gordon Ryrie, my successor as Editor and Medical Secretary of BELRA.

Dr. Ryrie has the two main requirements of an editor: he has a thorough mastery of the subject, having worked at leprosy in Malaya for some twenty years, and he has a flair for interesting and concise writing.

Leprosy Review has an important role to play, and we have frequently received letters of gratitude from readers, both medical and non-medical, engaged in leprosy work in lonely corners of the Empire.

I wish to thank all those who have contributed during the last ten years, and trust that they will continue their help. I hope also that others will assist by sending in articles, news, and other items which will be of help and interest to our readers.

I am particularly grateful to Sir Leonard Rogers who, besides helping in many other ways, took over my duties as Editor during the last four years of the war.

NOTE ON THE EARLIER WORK ON LEPROSY OF DR. ERNEST MUIR.

LEONARD ROGERS.

It was in 1920 that Dr. E. Muir accepted the post of whole-time research worker in leprosy in the newly founded Calcutta School of Tropical Medicine. The work was financed by an endowment fund which I had raised to provide for five additional research units.

In 1916 and 1917 I published, with coloured drawings and photos before and after treatment, very promising results in comparatively early cases of leprosy by the injection of soluble preparations of chaulmoogra oils, in place of the inefficient age-long oral use of these nauseating drugs. Muir at once took up the new method of treatment and was the first to confirm my work. I turned to him, therefore, as the best qualified man to continue my leprosy research in India when I went home on leave early in 1920 preparatory to retirement under the age rules.

Leprosy is a disease which shows such great variations in type, symptomology, degrees of mildness and severity and in its prolonged course, that only patient and prolonged investigations could allow the limits of the value of the improved method of treatment to be determined, and further technical improvements in the use of soluble chaulmoogra preparations to be worked out. Moreover, owing to the then small amount of interest of the medical profession in such an apparently hopeless disease as leprosy, no-one had any idea of its real incidence in India and other afflicted countries and its earlier stages were little known. How then were the earlier cases, which alone I had found to be amenable to treatment, to be discovered and induced to attend dispensaries for long periods for treatment?

These and other difficult problems awaited the attention of the newly constituted leprosy research unit in Calcutta. The following account will show how efficiently they were tackled by Muir and his assistants.

Muir's early work in Calcutta was mainly on two lines: firstly, further technical improvements in the use of chaulmoogra preparations for the injection treatment: and secondly, extensive surveys in selected areas to determine the true incidence of leprosy in India and to ascertain the most practical methods of extending the treatment of early cases of leprosy with a view to the ultimate control and reduction of the disease.

I had mainly used intramuscular and intravenous injections of weak solutions of the sodium salts of the lower melting points fatty acids of hydnocarpus wightiana oil. Its intravenous use was handicapped by its irritant effect causing blocking of the veins, but Muir got over the difficulty by the simple expedient of diluting the solution by drawing up some blood into the syringe before injecting the whole. A more important advance resulted from his finding that pure fresh hydnocarpus oil was unirritating when injected intramuscularly with a little creosote as an antiseptic. Both methods are very cheap, as compared with the use of ethyl esters of chaulmoogra oil, introduced in 1919 by American

workers in Hawaii, although the latter is very useful by intradermal injection into the skin lesions.

Muir and his assistants also carried out comprehensive house to house surveys for cases of leprosy in selected areas in each province of India with a total of two and a half million people examined. On comparing the data so obtained with the census figures for the same areas, which only included very advanced cases easily recognised at a glance by non-medical enumerators, they thus showed that when the early cases were included the true number amounted to four and a half times those returned at the last census. The proportion has since been placed by some as high as ten times. Fortunately some four-fifths of the early cases proved to be of nerve type, which are little, if at all, infective. They can therefore be treated as out-patients without being isolated. This patient enquiry enabled Muir to formulate his Propaganda-Survey-Treatment plan, under which the confidence of the people is first obtained by instructing them on the subject, house to house surveys are then carried out to disclose the true prevalence of the disease and special leprosy dispensaries are opened under doctors trained for the purpose at the Calcutta school. Within a few years hundreds of such clinics were opened all over India at which scores of thousands of early amenable cases were treated, and the people were also instructed on house isolation of infective cases in the villages. I had also advocated early in 1920 the establishment in every province of India of agricultural colonies for voluntary isolation, with adequate treatment, of the more highly infective nodular, or as they are now called, lepromatous cases; but lack of funds has prevented much advance in this essential feature of leprosy prohylaxis except in Madras.

Muir also availed himself of the abundant clinical material attending his Calcutta leprosy out-patient department to describe the phases and stages of the disease and especially its early little known stages. In the meantime I had spent three years in England on a comprehensive study of the literature of leprosy for some six decades, to ascertain the conditions favouring the spread of the disease and the most practical methods of its control. I then enlisted Muir's help in writing the clinical and pathological sections of a book on leprosy, to which I contributed sections on its history and distribution, epidemiology and communicability and on prophylaxis. This appeared in 1925 and reached a third edition in 1946; and it has influenced progress throughout the Britich Empire and far beyond it. In 1924 the British Empire Leprosy Relief Association was founded in London, and as the result of a visit to India in 1925 of its first Secretary, Mr. Frank Oldrieve, Lord

Reading, the then Viceroy, issued an appeal for an Indian branch. The success of this appeal enabled the Indian fund to take over financial responsibility for the Leprosy Research section of the Calcutta School of Tropical Medicine and for work in every province of India.

CLAMP METHOD TO OBTAIN CUTANEOUS LYMPH IN THE DIAGNOSIS OF LEPROSY.

H. C. DE SOUZA-ARAUJO

During research work conducted in Colombia in the early part of 1939 I had an opportunity of examining the Lleras method of obtaining skin lymph for the detection of Hansen bacilli. My Colombian colleagues used the common clamp of Pean to produce ischaemia of the affected part, thereafter obtaining lymph by a single puncture of the lesion.

Returning to Brazil I introduced the Lleras method with certain modifications. 1. The area of skin to be examined is, after sterilisation, gripped up with a haemostatic clamp of Pean (See fig. 1. Ref. fig. 2538 Catalogue Jetter and Scheerer). The blades are tightened till the first, second or third tooth of the handle is engaged according to the thickness of the skin. 2. The area of skin thus clamped, say 5 cms. long, becomes quite ischemic within a minute. It is then punctured deeply at four separate points with a large needle. 3. Four drops of clear lymph exuded from the sub-corium are collected each with a vaccination pen and smeared separately on a new and well cleaned slide. The slide requires a few hours to dry and is best covered with a Petri dish to avoid contamination from the air. 4. The slide is then stained by the usual Ziehl Neelsen method.

This modication of the Lleras method by eliciting four samples of material, proportionately increases the chances of finding bacilli as compared with single smear scraping methods.

When the lesion to be examined is situated in a region of the body characterised by dense subcutaneous tissue, e.g. the back, buttocks, etc., the technique is modified by using two clamps.

Where the lymph is obtained from a diffuse lepromatous lesion, the quantity of acid fast bacilli found in each microscopic field is enormous. Further, these bacilli stand out conspicuously owing

to the absence of tissue elements such as are found in scrapings.

It is suggested that this may be the method of choice for the detection of bacilli in tuberculoid or incharacteristic lesions. In my experience, bacilli may be found in all cases of tuberculoid leprosy even in some cases in bundles or globi by this method, athough such bacilli may not be demonstrable in ordinary histopathological sections.

The Lleras technique is an excellent method for the examination of institution cases for parole and in general in the control of treatment.

STAINING NODULES OF THE LEPROSY BACILLUS.

G. M. DE OLIVEIRA CASTRO

During the course of a study of the lepra bacillus I have elaborated two staining methods: Method I for staining structures which in this paper are called " bacilli nodules," or " nodules " for short, and which I believe to be identical with those seen by Albert Neisser as early as 1881 and represented in pen drawings in his " Weitere Beiträge zur Aetiologie der Lepra "; Method II which stains the well known " Coccothrix granules " fully reported by Adolpho Lutz in " Zur Morphologie des Mikroorganismus der Lepra " published in 1886.

I have obtained very good results with both. Method I has been submitted to the test of routine work with success, Method II is still under test and I hope to publish it in an early number of this *Leprosy Review*.

METHOD I.

By utilising the property of salts of precipitating the dye of a carbol-fuchsin solution, this method is connected with F. B. Cooper's modification of Ziehl-Neelsen, but it is different in other respects.

For the sake of clarity I shall begin by stating the chief points of Cooper's modification in his own words:

" Ammonium chloride, ammonium sulphate, barium chloride, calcium chloride, magnesium chloride, ferric chloride, lead acetate, mercuric chloride, sodium chloride, sodium dichromate and secondary sodium phosphate all cause the precipitation of the dye material from carbol-fuchsin when added in proper amounts. The

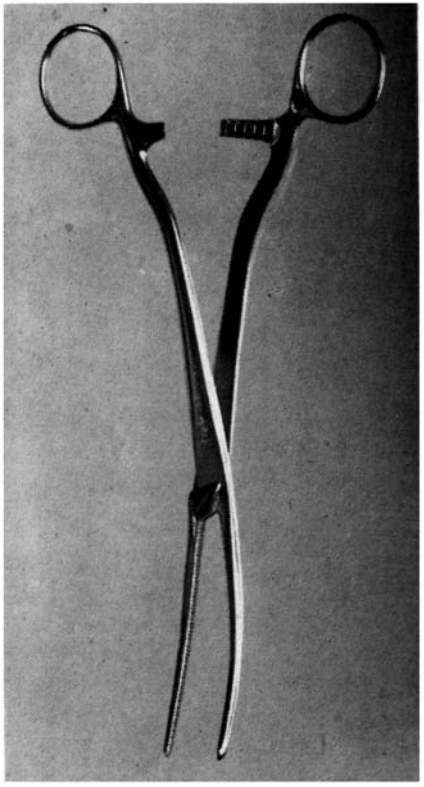

***Fig. 1.—Clamp** used for obtaining lymph*

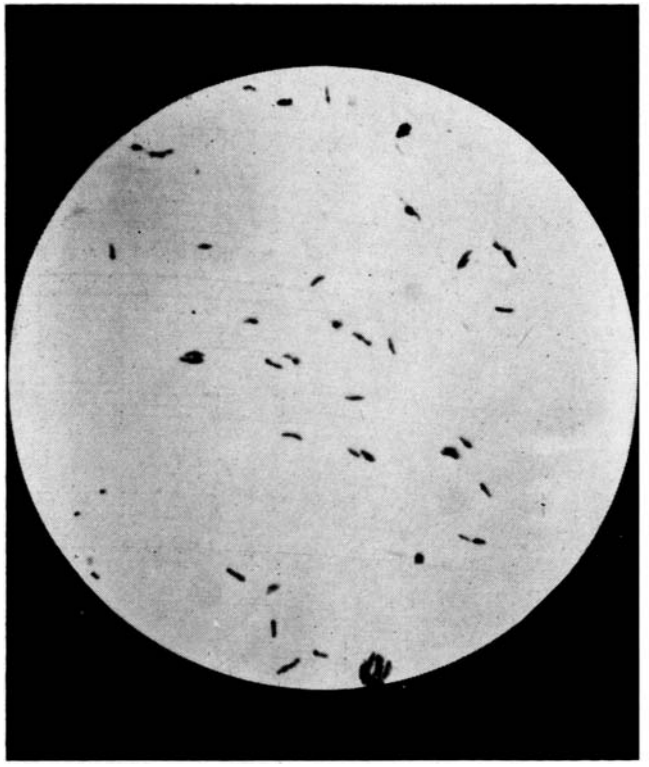

Fig. 2.—Bacilli stained by method of Dr. de Oliveira Castro

precipitate comes down at room temperature, but dissolves when warmed to 20-30 C., and remains in solution if that temperature is maintained." . . . . " Since the precipitant used makes no appreciable difference, sodium chloride was selected for the development of the modified stain. The amount necessary to give maximum staining was found to be 3 c.c. of a 10 per cent. solution per hundred cubic centimetres of carbol-fuchsin. Although this modified carbol-fuchsin precipitates at room temperature, it is stable if kept at incubator temperature, and keeps at least two months. ' . . . . " The technique for the modified stain, using the rapid method, is as follows: The slide is flooded with stain, steamed for four minutes and allowed to cool until the precipitate forms. This takes place in about two minutes, and may be hastened by gently blowing on the slide. The precipitate must be allowed to form, for on it depends the success of the method. It is then washed with tap water, decolorized from one to ten minutes in acid alcohol (5 c.c. of nitric acid, specific gravity 1.42, to 95 c.c. of 95 per cent ethyl alcohol); washed in water, then two minutes in 95 per cent ethyl alcohol; washed again, counterstained with Loeffler's methylene-blue for one minute, washed, dried and examined." . . . . ". . . . it was suggested that the methylene-blue, being an intense stain, might mask a number of bacilli by super-imposition and also by rendering the heavier portions of the smear non transparent. Various counterstains were tried and brilliant green 1 per cent. in 1:10,000 sodium hydroxide was selected, since such a solution failed to stain tubercle bacilli in ten minutes, gave transparent smears and stained secondary organisms pus and epithelial cells sufficiently to give nicely balanced fields in one to ten minutes."

I tried the salts with similar results to those of Cooper. It must be pointed out however that basic and acid salts, e.g. secondary sodium phosphate (Na_2HPO_4, pH8.7—9.5) and primary potassium phosphate (KH_2PO_4, pH 4.4—9.5), as well as neutral ones, cause immediate clouding of the dye irrespective of the different values of pH.

Potassium hydroxide, sodium hydroxide and ammonium hydroxide precipitate the dye, but hydrochloric acid, nitric acid and sulphuric acid do not.

As the element common to salts and bases which is not present in acids is the metallic cation, the precipitating action must be credited to this.

The precipitate dissolves when warmed, comes down if cooled again, and this reversible process may be repeated a number of times, after which it becomes more and more difficult to dissolve the precipitated dye.

Acids, in the concentrations used in decolorizing, ethyl alcohol and acetone easily dissolve the precipitated dye.

The precipitate, when washed from the salt solution, dissolves slowly in distilled water and in very diluted acids.

The precipitation of the dye before the acid-alcohol treatment is of the utmost importance. It may occur in Ziehl-Neelsen's method when, after heating the stain on the slide, sufficient time is allowed for it to form, which may take from a few minutes to more than an hour. When this happens the best results are obtained. On the other hand, if slides in which carbol-fuchsin remains perfectly clear are treated with acid-alcohol a great number of bacilli do not take the stain.

Having emphasised this basic point I shall summarise the experimental data which led me to a different process of treatment as compared with Cooper's staining technique.

The bacillary nodules always remain unstained when decolorising is done with nitric acid, in aqueous as well as in alcoholic solution; previously examined slides showed the bacilli with well stained nodules, using 95 per cent. ethyl alcohol as a second decolorising agent as proposed by Cooper, and treatment with alkalinised solutions to wash the stain from the nodules.

The study of stained smears obtained from excised lepromata, in which the very great number of bacilli and globi enables one to form an easy appreciation of the different results of various decolorising agents and precipitating salts used, led me to the following staining technique.

STAINING TECHNIQUE.

Add to the Ziehl-Neelsen's set of reagents a solution of an acid salt. I selected a 10 per cent. solution of primary potassium phosphate, KH_2PO_4, (with a small addition of calomel to avoid moulds).

Just before starting to stain, add 3 c.c. of the salt solution per hundred cubic centimeters of carbol-fuchsin, or in routine work 5 drops per 10 c.c. respectively.

Flood the slide with stain, steam for five minutes, allow to cool until clouding and the coming down of a precipitate.

Pour the precipitated solution from the slide, without troubling about the metallic green coating which is formed.

Without any washing in water decolorise in hydrochloric acid-ethyl alcohol (3 c.c. of hydrochloric acid, 97 c.c. of 96 per cent. ethyl alcohol), until the dye ceases to flow off and the slide is cleaned.

Counterstain in a diluted solution of methylene-blue (0.1 gm. of methylene-blue in 1,000 c.c. of water).

Wash again and dry.

The counterstaining must not be too prolonged, otherwise it interferes with the staining of the nodules. Half to one minute is sufficient, as well as for decolorising and washing. Smears with no counterstain are best for the study of bacillary nodules.

I use air dried smears as well as fixed and dehaemoglobinised ones in acetic-alcohol (acetic acid 25 c.c., ethyl alcohol 75 c.c.)

Results—The acid fast bacilli are selectively stained red, and show the nodules very dark red or brown; the cells and non acid fast bacteria take the blue colour. The nodules appear as more or less spherical structures of larger size than the diameter of the bacilli. They occur in small numbers, 1 to 3, rarely 4 or 5, in each bacillus. When 1 or 2 they are frequently at the ends of the bacillus, giving them a pin or a dumb-bell-like appearance. When in the middle portions, they appear as outstanding nodules or may be asymetrically placed on one side of the bacillus like drops hanging from a wire. These nodules are present in practically all bacilli.

I obtained the same results staining the tuberculosis bacillus from sputum smears.

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CHILD LEPROSY.

R. G. COCHRANE.

It affords me very great pleasure to give my contribution to this number of the Leprosy Review which is published as a commemoration number. To those who have been in leprosy work for more than twenty years, the name Muir means much more than an outstanding pioneer in leprosy. We who were privileged to be his students can appreciate his work, his thoroughness and his perseverance. Many advances have been made since the days

when Muir with courage and persistence championed the cause of leprosy in India and in so doing gave leprosy her rightful place in preventive medicine. Muir made it possible to progress, until to-day leprosy is beginning to be viewed as an ordinary disease, first and foremost as a medical problem and not as a social stigma.

Muir, and earlier Rogers, recognised the importance of child leprosy and Muir's insistence on adequate attention being given to leprosy in children stimulated the establishment of a centre for the investigation of child leprosy in Madras. While factors beyond our control have prevented the development of work in child leprosy to its full, sufficient information has been amassed to convince us that when Muir, in the early days, emphasised child leprosy he and the earlier pioneers were pointing the way not only to a better understanding of the disease, but also suggesting the key which would open to us possibilities of its ultimate control.

In taking as my subject child leprosy in this special number of the *Leprosy Review* I wish briefly to stress its importance in relation to (1) Epidemiology (2) Pathology and (3) Treatment.

It is a truism to state that no system of prevention of leprosy can possibly succeed without an adequate study of the epidemiology of the disease. In our endeavour to organise adequate measures of control in South India our policies and opinions have been influenced largely by our study of child leprosy especially in relation to epidemiology. We have held the opinion for many years that only a certain amount of child leprosy is serious from the preventive aspect, and that leprosy in South India can in a significant proportion of cases be looked upon as a benign non-progressive disease. Evidence for this is furnished in a publication which is already in the press. It can be said that from the point of view of the development of more serious leprosy—i.e., lepromatous leprosy—practical consideration need only be given to (1) Simple neural leprosy with multiple hypopigmented macules (2) Pre-lepromatous lesions. The existence of this latter condition has been doubted by certain workers but Muir (1936) himself drew attention to the existence of these lesions emphasising their slight clinical signs, their serious prognosis and their importance in the development and spread of leprosy in a community. While only perhaps five or at the most ten per cent of all child cases in a highly endemic area can be placed in this category, yet from observations over the past ten years it has been confirmed that not only do the majority of such cases develop lepromatous leprosy in later life, but these cases more often arise in families where there is the closest contact from early years with open cases. In fact it can be stated with considerable force that if more attention

were focussed on the real cause of the spread of leprosy—the infective case in the house—more success would be achieved. Further, a study of the incidence of child leprosy, we believe, gives a clue not only to the degree of endemicity, but to the effectiveness of measures of control.

I have stressed for many years the need for a better understanding of the pathology of leprosy especially in relation to the skin. I am more convinced than ever that the corium of the skin is an area of stategic importance in leprosy and that the M. Leprae elsewhere are mainly saprophytes living in a state of commensalism in the reticulo-endothelial system of the body. In other words, without multiplication and spread of the organism in the skin there can be no progressive disease. A study of the tissue reactions in the skin especially in children gives much support to this contention; for, it is in childhood that the earliest lesions are seen and their progress can be traced from the stage where there are no bacilli in the skin to that of active multiplication and dissemination of the organism in the corium of the skin resulting in widespread dissemination of the M. Leprae throughout the reticulo-endothelial system. On the other hand, we have observed over a period of many years lesions which have spontaneously disappeared in childhood and the one fact which has impressed us is the apparent inability, in some instances, of the M. Leprae to multiply and spread in the skin. Hence the disease has shown spontaneous resolution. Contrary to earlier opinion we believe that diet, predisposing diseases, and debility play little or no part in causation. The cause is to be found in close association *within the house* with an open case during childhood. As suggested, if more attention were paid to this aspect of prevention and less to unproved and hypothetical theories, we would to-day be nearer the solution of this age long problem.

The study of child leprosy has led, we believe, to a clearer conception of the pathology of the disease. It is only possible in a short article to indicate how our studies have thrown more light on the pathological processes in relation to leprosy. The idea that leprosy is a self-healing disease is not a new one, and Muir re-emphasised the importance of this early observation. It was he who coined the term " Burnt out " visualising the disease as a fire which smoulders, rises to a flame and then slowly splutters out in dying embers. We are beginning to realise however, that, to continue the simile, at times the fire is quenched even before it has a chance to rage, and that frequently leprosy becomes spontaneously " cured " leaving no traces that it has ever been there. At other times the fire continues to smoulder and then

splutters out without ever rising to a flame. Thus it is only the exceptional case which goes through the whole course of the disease and ends up as a secondary neural case.

The study of child leprosy which has been undertaken in Madras has indicated that the skin is the main defensive organ in leprosy and that if as in tuberculoid leprosy an active tissue reaction can be stimulated anchoring or shutting off the multiplying bacilli in the corium of the skin then progressive leprosy cannot develop. If on the other hand no active tissue immunity is present, then there is a grave danger of the bacilli multiplying widely, breaking through the skin barrier and then becoming disseminated in a widespread manner throughout the reticulo-endothelial system. This is not the place to discuss classification and the development of lesions but we cannot accept the view that tuberculoid leprosy subsequently develops into leproma. We believe that it is only those which show atypical features which so develop.

Turning now to the question of treatment I should like to state particularly in the case of child leprosy that drugs which aim at the destruction of M. Leprae in the body have only a limited place in the treatment of leprosy. When one is faced with a case of child leprosy three questions should be uppermost in one's mind.

1. Does the child really need treatment?
2. What are our chances of preventing deformity?
3. How can we prevent the spread and multiplication of M. Leprae throughout the body?

There are many cases of child leprosy which are being quite unnecessarily submitted to prolonged courses of injections which are extremely painful especially if intradermal injections are given. If treatment is necessary then it must be given and given vigorously, but in cases of benign neural leprosy, apart from measures for causing the lesions to scar, either by excision—if only one—or by local applications, or by intradermal injections, no other measures are necessary. On the other hand, long courses of injections are sometimes given to neural cases when one's attention might better be employed in devising and studying methods whereby deformity can be prevented and, if present, rendered less disabling.

For lepromatous leprosy the standard method of treatment still consists of injections of hydnocarpus (chaulmoogra) oil preparations preferably concentrating on intradermal injections. I am aware that the recently discovered preparation of diamino-diphenyl sulphone, especially promin and diasone have

received much publicity. Two warnings must be issued in connection with these drugs (1) They are toxic (2) They must only be administered under very careful conditions where regular blood levels and haemoglobin estimations can be carried out. Unless care is exercised in this direction tragedies may result.

Admittedly our results with the chaulmoogra derivatives in advanced lepromatous leprosy are not satisfactory, but in our disappointment with these remedies, let us not fall into the error which is so often committed by showing excessive enthusiasm for the newest remedy which admittedly is promising but is not yet fully tried. There is no more tragic experience for the leper for whom little can be done than the excitation of hopes which may be dashed to the ground as a result of more prolonged trial and experience.

A word of warning at this point must be added. If the sulphone preparations are found to be effective in leprosy it must be remembered that their use will largely be confined to lepromatous cases; and even if a remedy were found which would permanently heal lepromatous leprosy the leprosy problem would not be solved over night. Curative measures have always taken precedence over preventive ones. These remarks apply particularly to children for no curative remedies can overcome disability due to nerve damage or muscular astrophy. Neither can specific remedies alleviate permanent damage to structures such as the eye, or cure trophic ulceration. This is a wide and neglected aspect wherein the ophthalmologist, the orthopedic surgeon and the neurologist will find almost a virgin field. Indeed it is high time we thought in terms of the whole problem for, apart from the specific medical and surgical problems, vast though they are, little or no consideration has been given to welfare or social service, to betterment of village conditions, and propaganda efforts to educate the public not only in preventive measures which must be taken in the home, but to a better understanding of the disease.

To one who has worked for nearly a quarter of a century in leprosy and has had the privilege of drawing inspirations from such stalwarts as Drs. Muir, Wade, Denny and Wayson, it appears as if we are just on the threshold of something new. Let us remember however, that as in medicine the whole of man must be our consideration; so in leprosy this whole view must be ours. There is no greater danger to-day than that on the eve perhaps of outstanding success we lose our perpective and thereby deprive ourselves of the rich fruit which will be one day the reward of those who strive.

Ref. Muir (1936) "Juvenile Leprosy" I.L.J. *IV* 45.

COMMENTS ON THE HISTORY OF LEPROSY.

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JOHN LOWE.

For a number of years the writer has been collecting material on the history of leprosy. No comprehensive acount of this subject has been traced, although there are numerous excellent papers on individual countries and periods. The writer has, however, been struck by the lack of sound evidence to support statements sometimes made on this subject, even by well known writers. These statements are apparently copied without verification from earlier to later editions and from older to newer books.

It was in the late eighteenth century and in the nineteenth century that the history of leprosy aroused considerable interest, and several publications on the subject appeared. The first history, and in many ways the best, appears to have been that of Hensler (1790), and later historians included Shapter, Simpson, Virchow, Kaposi, Munro, Creighton, Newman and others, Some statements made in the earlier books have since been shown to be untrue, but they are still quoted from time to time.

Most writers have expressed the view that in some countries in ancient times and in mediaeval Europe, leprosy was common, but early in the nineteenth century Shapter, and late in the nineteenth century Creighton, and to some extent Newman, expressed the view that the prevalence of leprosy in Europe in the middle ages might have been greatly exaggerated. A more recent writer in the same vein has been McArthur who used the following words regarding the published statements regarding the history of leprosy, ' Oh, history, what crimes have been committed in thy name,'

Actually the present writer thinks that this critical attitude is sometimes carried too far, and that the evidence indicates that leprosy in the past was both common and severe in Europe as well as Asia, but there is no doubt that there has been written much bad history of leprosy. In a new (1942) edition of a standard American book on tropical medicine, the chapter on leprosy includes a historical section in which some of the old mistakes have been repeated.

In the present article no attempt is made to discuss fully the history of leprosy, for it is a vast subject. It is proposed here to discuss a few of the commonest misconceptions about the ancient

history of leprosy in the world as a whole, to make some general comments on the subject, and to adopt the principle that in ancient literature the use of a word which might have been used at that time for leprosy is of no value as evidence unless supported by clinical details definitely suggesting if not clearly indicating leprosy.

Leprosy in ancient India.

It has been stated by many writers that leprosy is mentioned in the Vedic writings of India. The Rig Veda and the Athava Veda have been cited. Rogers and Muir state that leprosy is mentioned as *kustha* in the Vedas of about 1400 B.C. although in the recent edition they say that it is not sure that *kustha* meant leprosy. 'Kustha' (or more correctly *Kushtha*) in ancient Hindu medicine meant skin diseases in general,one of which was leprosy. In the Vedic writings the word *kushtha* appears in a very few places, and it is not certain that leprosy is meant. There is, however, no doubt that leprosy was well known and described in ancient India. Many writers have cited the *Susruth Samhita* as mentioning leprosy and Dharmendra has recently quoted and translated these passages from the *Susruth Samhita* which have a bearing on this subject. The present recension of the *Susruth Samhita* was probably written about 600 B.C. but it embodies traditional knowledge from still more ancient times. *Susruth Samhita* describes treatment of leprosy with chaulmoogra oil.

This is actually the most authentic ancient reference which I have been able to trace, and it is also in many ways the most accurate and complete of the old descriptions. Under different heads it describes most of the signs and symptoms of leprosy even in its milder forms with which we are familiar to-day. This fact suggests the possibility that in ancient times, as in the present times, leprosy in its milder forms may have been more common in India than in some other countries.

It has sometimes been stated by writers in India that the Laws of Manu contain definite instructions about the prophylaxis of leprosy. The Laws of Manu (the *Manava Dharma Sastra*) have been attributed by various European scholars to various periods between 500 and 1300 B,C. Sir William Jones placed the writing between 1200 and 500 B.C. Max Muller was of opinion that in its present form it is of relatively recent date but that its origin is much more ancient. In India it is popularly regarded as being of extreme antiquity.

Possible references to leprosy are made in four places. The Sanskrit word *shitri* almost certainly meant leucoderma and *kushtha*

meant skin diseases in general, prominent among which was possibly or probably leprosy. In Book III, sloka 161, a man suffering from *shitri* in included among the list of those who should not be present at religious ceremonies. In the same book, sloka 177, it is stated that the presence of a man who suffers from *shitri* causes the giver of the feast to lose the ' merit ' acquired by entertaining one hundred suitable persons (Brahmans, etc.). In Book VIII, sloka 205, it is stated that if a man giving a girl in marriage has openly declared her blemishes, that she is insane, afflicted with *kushtha*, or not a virgin, that man is not liable to punishment. In Book III, sloka 7, states that a ' twice-born ' in choosing a wife should carefully avoid families whose members are subject, among other things, to *shitri* or *kushtha*. These are the only references to leprosy detected in the translation of G. Buhler. A Sanskrit scholar has verified for me the accuracy of the above statement.

These passages of the Laws of Manu are therefore not regarded as conclusive proof of the prevalence of leprosy, but when studied in relation to the Hindu medical writings of a similar period, they afford strong evidence that leprosy was common. There is, however, no evidence of the truth of the assertion recently made in a medical journal in India that in the Laws of Manu the prophylaxis of leprosy is well described.

Leprosy in ancient China and Japan.

In the literature of ancient China there is little clear evidence of the existence of leprosy. A study of the history of Chinese medicine by Wong and Wu leads to the following conclusions:—

The Chinese medical classic the Nei Ching, attributed by Wong and Wu to the period of 220 B.C. but attributed by tradition to Huang Ti (2700 to 2600B.C,), contains four possible references to leprosy under the two names Ta feng and Li feng. None of the four references clearly indicates leprosy although numbness is mentioned in one of them. There is also an ancient tradition that one of Confucius' disciples about 600 B.C. died of leprosy, but here again there can be no certainty. In the third century A.D. there is description of a disease with numbness which is suggestive of leprosy, but it is not until the seventh century A.D. that fairly definite clinical descriptions of leprosy appeared, and it is stated that the disease was common, one record mentioning 600 cases treated and one in ten cured. During this and the succeeding centuries ostracism of lepers was practised, and in the fifteenth century is made the first mention of treatment of leprosy by chaulmoogra oil at least 2,000 years after it was used in India. The treatments mentioned in ancient Chinese medical writings for

leprosy include purgatives, diaphoretics and diuretics, arsenic, and snake and scorpion venom.

In Japan according to the Japanese writers Tashiro, Kitasato, and Mitsuda, leprosy is described in the literature of the eighth and ninth centuries, A.D. Japanese medicine seems to have been much influenced, if not dominated, by Chinese medicine. It appears that there is little foundation for the statement made in the text-book of tropical medicine mentioned above, that in Japan it (leprosy) seems to have been recorded first in 1250 B.C.'. This is probably a copyist's error. Newman gives the date 1250 A.D. for Japan.

Leprosy in Biblical writing.

The whole question of leprosy in Biblical writings has been discussed by many authors and the matter can be discussed only briefly here. Writers of the middle ages and later mostly assumed that the *zaraath* of the Old Testament and *lepra* of the New Testament were leprosy as it was known in the middle ages and as it is known to-day. Some recent writers have however challenged this view and there has been much discussion on this point. Lie discusses the matter well. Among the many interesting points one is that ' Zaraath ' even if it included leprosy could only have covered the ' maculo-anaesthetic ' variety of leprosy and that nowhere in the Bible is there any mention of the ' nodular ' form of the disease which looms so large in the ancient literature of leprosy.

Lie concludes that a study of the Bible does not prove that leprosy existed among the ancient Hebrews but since the Jews spent long in Egypt ' which certainly must have been infected with leprosy ' he finds it difficult to believe that leprosy was not found among the Jews.

To this brief discussion of the subject about which there has been much controversy, I will add only a few remarks. As we see later there is no conclusive proof of the presence of leprosy in ancient Egypt although it was possibly and even probably prevalent. According to various authors Manetho is quoted by Josephus (De Antiquitate Judaeorum) as recording 90,000 cases of leprosy among the Jews, an incredibly high number for true leprosy.

Finally, nowhere in the Bible is there any clinical description corresponding to leprosy as we know it to-day, no mention of numbness and loss of skin sensation, or of the manifestations of leprosy of the ' nodular ' type such as are found in the ancient literature of India and of some other countries. The 1942 edition

of the standard textbook on tropical diseases states ' In Leviticus 13 and 14, truly remarkable passages regarding the diagnosis and prevention of leprosy are to be found,' The passages are remarkable but they do not describe leprosy. They describe skin diseases, and from the administrative point of view divide the patients into three classes: those to be isolated indefinitely; those to be isolated for seven days at a time; and those not needing isolation. If our leprosy appears at all, it is in the last group! In Leviticus 13 the chief criterion for a diagnosis of leprosy is whiteness of patches of the skin and more particularly of the hair on the patches. Such patients are to be isolated indefinitely. Now leprous patches are not white, and, most important, the hair is not white. This whitening of the hair in white patches of the skin is very suggestive and almost diagnostic of leucoderma. Moreover, the patches of leprosy are only partly depigmented; but verse 38 says that if a person has patches which are dull white, he is clean, that is, not suffering from leprosy, and need not be isolated.

It appears therefore that the ' leprosy ' of Leviticus 13 was not our leprosy, and was much more probably leucoderma.

Leprosy in ancient Egypt.

In the literature of the last seventy years there are numerous references to leprosy as being mentioned and described in ancient Egyptian writings. Munro writing in 1876 mentions an Egyptian record of the time of Ramesis II about 1350 B.C. describing the occurrence of leprosy among the Negro slaves from the Sudan and Dafur. This record is also mentioned by Rogers and Muir although they state that its authenticity is disputed. Newman writing in 1895 goes even further back and states without any reference that ' it existed in Egypt in the reign of Husapti at least 3000 years B.C.'. The recent text-book above mentioned gives the date as 4600 B.C. It has repeatedly been said that leprosy (like many other diseases!) is described under the term *Uchedu* in the Ebers papyrus written about 1550 B.C. Sauton writing in 1901 recorded the existence in the Cairo Museum of stone statues belonging to the early dynasties of the Pharaohs, which show typical leprous mutilations, Engel Bey reported in 1890 that the Berlin papyrus contained a treatise on leprosy of a very early period, that is of about the time of the fifth Pharaoh. This is a selection of statements that have been made by different writers at different times. Others could be quoted.

A critical examination of these records, however, makes it exceedingly doubtful whether a single one is authentic. Engel Bey,

who worked for many years in Egypt in close touch with Egyptologists, wrote in 1903 correcting his earlier statements about the Berlin papyrus mentioning leprosy, and said that no particulars of the symptoms of the disease are given. He reported a fruitless search to discover the statues showing leprous mutilations reported by Sauton to be in the Cairo Museum. He did not produce any definite record of leprosy in ancient Egyptian writings or monuments, although he stated, on what grounds it is not clear, that leprosy existed in Egypt long before the Christian era..

Ebbel has made a study of the subject including particularly the Ebers papyrus. He finds that the disease described under the names of *Uchedu* does not correspond with leprosy, and he thinks that the translation of this word as leprosy is wrong. He states however that in another part of the same papyrus, leprosy is described under the name ' Chons ' swelling.' The passage he cites indicates that this is mainly an affection of limbs. The present writer finds that the identification of leprosy with either *Uchedu* or ' Chons ' swelling' is unsatisfactory, the distinguishing features of leprosy not even being mentioned.

Unless more recent work has produced new evidence, it appears that we have no definite proof that leprosy was common or even known in ancient Egypt. We have to come to far later times for the first definite reference to leprosy in Egypt.

Leprosy in royal persons in Europe in the Middle Ages.

It is frequently stated that Robert the Bruce suffered from and died of leprosy, but it is by no means certain that he did. Both Simpson and McArthur studied the historical documents but arrived at opposite conclusions. During their lives or shortly afterwards, reports were made that Henry III and Henry IV of England suffered from leprosy, but, as McArthur has pointed out, statements of this kind made by personal enemies are of no historical value. Simpson, however, rightly said that these reports at any rate clearly indicate that in the middle ages leprosy was not considered incompatible with the highest rank and wealth, and we have authentic records of leprosy in such persons.

Possibly the best authenticated case is that of King Baldwin the Fourth of Jerusalem who was related to the kings of England. Jeanselme gives interesting abstracts from historians of the period who describe in detail how Baldwin when a child developed anaesthesia of the limbs and how by the age of 23 he had become blind, his hands and feet had become crippled and mutilated and putrescent, He resigned his kingly powers and shortly afterwards died.

Leprosy in Mediaeval Europe.

Mediaeval medical writings leave no room for doubt that the leprosy of the middle ages was our leprosy of to-day.

Again and again during the last hundred years the statement has been made that the number of leper houses in Christian Europe in the middle ages was 19,000 and this statement once more appears in the latest book on tropical medicine mentioned above. This statement possibly originated from Hensler's writings in 1790 and it appears to be based on a quotation from Matthew Paris. (Matthew Paris was a chronicler who lived from 1200 to 1259 and was, according to Green, the last and the greatest of the monastic historians of England.) In 1903 Pernet stated that as early as 1819 it was pointed out by an unknown writer on leprosy in Rees' Encyclopaedia that the statement was based on a mistranslation of a passage in Matthew Paris' ' History of the English up to 1244.' The original Latin sentence runs as follows: ' Habent nisuper Templari in Christianitate novem millia maneriorum, Hospitalarii vero novem decim '. This sentence apparently means that the Knights Templars in Christendom held 9,000 manors and Knights Hospitallers 19,000 (the second ' millia ' being understood). The word for manor seems to have been translated as leper house, with no justification. It is true that the Knights Hospitallers (or the Knights of St. Lazarus) administered many of the leper houses in Europe, and that the order existed for this purpose, but this does not justify the statement that there were 19,000 leper houses. Ehlers, however, pointed out that the number of leper houses was probably not much smaller than the number of manors, since many if not most manors would include a leper house; that in the thirteenth century 3,000 of the leper houses in Europe were under the ' commanderie magistrale ' of Boigny, the headquarters of the order of Knights Hospitallers, that at the time of St. Louis there were officially recorded 1,502 leper houses in France and there were probably others also; and that even in 1693 when leprosy had practically disappeared, the order for the closure of the leper houses in France affected 1,133 establishments the income of which was thereafter devoted to other charitable purposes.

Virchow, as quoted by Rogers and Muir, recorded that there were 636 leper houses in Italy, Verdun and Maestricht. Newman gave a list of 200 leper houses in England and Wales alone, and stated that it was incomplete, as it undoubtedly was. Pooth traced records of nineteen leper houses within one small area of Eastern Germany which to-day has a population of only 150,000 and was then much less thickly populated.

The standard English book on leprosy is Rogers and Muir

who in their historical section are in general soundly sceptical, but in their last edition they appear to have adopted perhaps rather an excess of scepticism regarding the number of leper houses and the prevalence of leprosy. They state for example that the number 2,000 often quoted for leper houses in France ' has been discredited by Jeanselme ' but a study of Jeanselme's big work on leprosy does not bear this out. Jeanselme himself gives a list of over 900 leper houses in France and this list makes no claim to completeness and applies only to certain parts of France.

Rogers and Muir also quote the estimate of Creighton of the extent of leprosy in England in the middle ages at its worst period: ' There might have been a leper in a village here and there, one or two in a market town, a dozen or more in a city, a score or so in a whole diocese. Thus in the records of the city of Gloucester, under the date 20 October 1273, three persons are mentioned by name—a man and two women—as being leprous and as dwelling within the town to the great hurt and prejudice of the inhabitants.

The same author Creighton in his ' History of Epidemics in Britain ' adopted the attitude that while the existence of leper houses in England in the middle ages cannot be denied, it was attributable not so much to the prevalence of leprosy, as to the misguided piety of the period. He seems to have thought that the high figures often given for the number of leper houses is attributable mainly to the misguided enthusiasm of romantic historians of modern times, whom he accuses of labelling as leper house every charitable institution of doubtful nature of which they can find any record in mediaeval writings.

Creighton's statement appears to be very one-sided. It mentions only the three known lepers living in the town of Gloucester but does not mention the two leper houses outside the town which according to Bigland's History of Gloucester (quoted by Newman) were founded in the twelfth century under a charter. We know that the population of Gloucester at that time was only about 4,000. We know that the city of Norwich in the fourteenth century with the population of a few thousands (the generally accepted figure is about 7,500) had no less than six leper houses. We know that the diocese of Exeter at the beginning of the fourteenth century had thirty-nine leper houses, for there is still extant (Button) the will of Thomas Button, Bishop of Exeter who died in 1307 and left 200 legacies including 40 legacies to lepers lodged in 39 leper houses in the diocese; this is confirmed by the statement of the executors of this will (Boggis).

It is interesting to note that Newman's list of the 200 leper houses in England and Wales includes only one-third of these 39

leper houses in the diocese of Exeter, but that it does include five or six other leper houses which were established later in this diocese. It therefore appears that the number of leper houses in the diocese altogether totalled even more than 39, and that Newman's list of 200 leper houses for England and Wales is, for this area, very incomplete and probably for other areas also. It is therefore considered that the number of leper houses in England has not been exaggerated.

Some writers have expressed the view that not only has the number of leper houses been exaggerated but also their size and the extent to which they were actually used for cases of leprosy and that therefore ideas about the prevalence of leprosy in the middle ages in Europe are exaggerated.

As we have seen, the number of 19,000 often given for the number of leper houses in Europe in the thirteenth century is wrong and based on a mistranslation, but it also appears that the number was probably at least several thousands. There is no doubt that most of the leper houses was small but we know that some of them had accommodation for over fifty patients and, although it cannot be quoted fully here, good historical evidence exists for the belief that the leper houses were used to a considerable extent for genuine cases of leprosy. Even when they were not so used, it was often not because there were no lepers, but because the funds were being misappropriated by kings, barons, local lords and the clergy!

It has often been suggested that inaccurate diagnosis must have led to the committal to leper houses of persons who were not suffering from leprosy and this undoubtedly must have occurred. Nevertheless, a study of the mediaeval medical writings on the subject such as those of Guy de Chauliac indicates that the need for care in this matter was realised. This writer describes the unequivocal signs of leprosy which alone justify the diagnosis of leprosy and committal to a leper house, and it is interesting to note that he wrote as though a diagnosis of leprosy was usually if not always followed by such a committal. His unequivocal signs of leprosy however are such as are seen only in what we should call very advanced cases. It is obvious that if this was the criterion for a diagnosis, there must have been very many cases of leprosy outside the leper houses.

Another matter stressed by a few writers is the frequency with which other diseases such as secondary and tertiary syphilis must have been wrongly diagnosed as leprosy, At a later date this was undoubtedly true, but at the time that leprosy was at its height in Europe and most of the leper houses were being built, syphilis was

either rare or absent from western Europe. Most historians are in agreement that leprosy was at its height about the thirteenth century but that syphilis did not appear in western Europe in appreciable amount until much later.

Another factor that is often overlooked is the small size of the population of European countries particularly England at the time that leprosy was at its height. In England, for example, in the latter part of the fourteenth century the total population was probably not more than three millions. Actually the figure generally accepted by historians for the year 1377 is just over 2½ millions. This figure is from calculations based on the figures of the number of persons paying the poll tax of that year. There were in England at that time only 41 towns with more than 1,000 people, only 22 with more than 3,000, only 10 with more than 5,000, and only 3 with more than 10,000, namely London, York and Bristol with 40 thousands, 13 thousands and 12 thousands respectively. This, however, was in the period following the Black Death, which killed, it is said, one-third of the whole population of England and probably a higher proportion of the population of the towns. Nevertheless, it is certain that many towns were little more than large villages centred round a castle or an abbey. In spite of their small size, nearly all the towns had one, and some two or more leper houses, Norwich having no less than six.

There is much more which might be said on the subject. A general consideration of the available literature has led the writer to the view that the prevalence of leprosy in England and in fact in mediaeval Europe was very considerable. Nevertheless, there is no adequate historical evidence to justify the impression given by some historians such as Green that leprosy affected a large section of the population and became a scourge and not much less serious in its way than the Black Death.

In no large area of the world even under conditions most favourable to it does the incidence of leprosy to-day rise much above 5% and a much more usual incidence is about 1%. It seems that the incidence of leprosy in the middle ages in Europe was probably no higher than it is to-day in certain parts of Africa, Asia and South America and was possibly much lower, although of course any accurate estimation is out of the question.

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REGRESSIVE CHANGES IN LEPROSY UNDER PROMIN THERAPY.

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INTRODUCTION.

During the past four years continuous intensive treatment with promin has been carried out in a considerable number of patients at the National Leprosarium, as reported by Faget and others. These patients have been receiving daily intravenous doses, usually 5.0 grams, with rest intervals of one week for each three of treatment, in some cases for more than four years. It has been the continued experience of all connected with this work that the treatment is beneficial in most cases. Although clinical improvement is slow, and bacterioscopic improvement even more slow, relapses

have been extremely rare, and the progress of improvement has been steady in most instances.

The purpose of this paper is to report biopsy findings in 32 patients who have been receiving the drug during periods of 18 months to 4 years, in order to determine the tissue changes associated with remission of the active disease process. In all cases the lesions which were selected for biopsy were those which were most prominent over the trunk and extremities, lesions of the face being avoided. In about half the cases these represent persistent small lesions in individuals in whom most original lesions were no longer clinically apparent. In all cases the biopsied lesions had undergone varied degrees of clinical regression. In four cases in which the biopsied lesions were still frank elevated lepromatous nodules, rich in organisms, there had been marked improvement in these lesions clinically, consisting of disappearance of signs of inflammation, and 50 per cent or more decrease in size of the lesions themselves. The lesions studied can thus be considered representative of the more severe, or more active, existent in the individual patients,

In 14 cases biopsies made two to three years prior to the present study were available for comparision. In eight of these the same area was subjected to the second biopsy, and in three cases the same lesion.

Paraffin sections were stained with hematoxylin and eosin, and frozen sections with Sudan IV. Frozen sections were also used for acid-fast stains to insure total staining of organisms present, and several such sections were studied in each case.

RESULTS.

Bacterioscopic Findings. All the cases had been bacterioscopically positive at the beginning of treatment, but 10, or 31 per cent, of the lesions biopsied after treatment are free of demonstrable organisms. Five of the positive cases had had occasional negative smears from the skin of other parts of the body. In one case in which the biopsied lesion is free of organisms, other lesions in the body are positive by smear.

From comparision with previous biopsies it is clear that there is not only decrease in size of the lesions, but also decrease in average numbers of bacilli per cell. In only three cases are the vacuolated cells heavily laden with bacilli. For the most part, in the treated lesions the number of bacilli per cell is small; the bacilli are often feeble in their staining propensities. The degree to which large infiltrations may atrophy, leaving little behind, is astonishing in several of the cases.

In six cases the presence of large masses of bacilli in globi is an outstanding feature of the lesion. In five of these the large numbers of bacilli in globi stand in moderate contrast to the small numbers of poorly staining organisms in adjacent vacuolated cells. In these cases there is an obvious persistence, or even increase, of bacilli in the globi, in contrast to simultaneous decrease in vacuolated cells. It is also noted that small globi, and bundles of bacilli in typical cigar-packs, commonly associated with progress of lesions, are extremely rare in the treated cases.

However there are changes in several of these cases, as well as in some other lesions, which indicate clearly loss of bacilli from globi, so that the phenomenon of persistence of bacilli in globi is not uniform. Cowdry[2] showed that the investing "membranes" of giant globi consist for the most part of thinned out giant cells. The correctness of this is well seen in several of the present cases in which giant cells enclose old global vacuolated masses which have shrunk greatly in size and lost most of the organisms, but still retain the global matrix of the globus, with perfect preservation of the giant cells themselves.

The bacterioscopic results of examination of skin smears in 100 cases after promin treatment for 2 to 4 years are presented in Fig. 1. The data are condensed from the results of examination of more than 2,000 smears made according to the commonly used technique of examination of small amounts of material, mostly tissue juices, obtained from a minute incision into the cutaneous lesions.

It is observed that the most significant drop in numbers of bacilli found in the lesions occurs in the fourth year of treatment. In a group of 42 patients who have finished nearly four years of treatment, 21, or 50 per cent, have shown persistently negative smears during the fourth year, whereas none of these patients had wholly negative monthly smears during the third year of treatment.

The group of twenty-six patients on promin treatment for the past two years only shows a comparatively greater degree of improvement in two years, which may be partly accounted for by larger doses and more continuous treatment than were used at the beginning of the work.

Atrophic Changes. With a single exception all the lesions show extensive evidence of atrophy: atrophy of the epidermis, of sweat glands, of nerves, hair follicles, and so on, and most interestingly, of the vacuolated cells themselves.

The single exception deserves comment. This is the case of a white woman 40 years old, with leprosy of 11 years duration,

consisting largely of numerous small discrete nodules scattered over most of the skin of the body. Under promin treatment for three years, only a few of the smallest nodules have completely disappeared, but all have decreased greatly in size, including that taken for biopsy. This lesion, however, shows most numerous leprous lesions, and much fewer in slightly deeper areas, there being no bundles of bacilli, or globi.

This case is the exception. In all the others there is much decrease in size of the focal infiltrations about the various structures and appendages of the skin which make up the common lepromatous infiltration, One of the features, which readily demonstrates shrinkage from a previous much greater size, consists of the persistence of many small blood vessels in the lesion, even after most of the advantitious cells have disappeared. This is a constant feature seen in varying degree in nearly all cases, sometimes only in the more superficial foci, sometimes throughout the lesion.

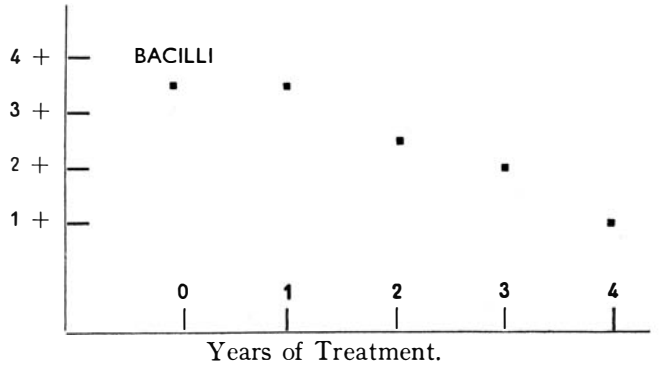

Fig. 1. Bacterioscopy of leprous lesions after prolonged promin therapy.

The atrophy of the lesion also appears frequently as simple loss of cells from the foci, leaving the remaining cells much more distinct. In the ordinary chronically active lepromatous infiltration, distinction of individual vacuolated cells is difficult. In the atrophic foci the single cells are often plainly seen, separated from one another by a little edema fluid, or by infiltrating lymphocytes. It is found that under these conditions a majority of the vacuolated cells have more than one nucleus.

Another feature associated with atrophy is a greatly increased number of lymphocytes in certain foci. It is never certain, of course, whether these are increased numbers, or residual lymphocytes made more prominent by loss of vacuolated cells. In the case of plasma cells, which in small numbers are a routine feature

of lepromatous infiltrations, the latter seems definitely to be the case.

Atrophy of the Epidermis.—The epidermis covering lepromatous lesions is regularly thinned out, and the papillae are flattened. Following regression of the lesion, this change is often permanent, as has been noted of maculo-anaesthetic lesions in the past, and as is evident in the permanent alteration in the character of the epidermis clinically in many cases. In other cases various degrees of formation of new rete pegs occur, sometimes producing a definite acanthotic change.

Atrophy of Sweat Glands.—Infiltrative lepromatous lesions almost invariably involve the coil glands by embedding them in granulomatous tissue, leading to atrophy and loss of function, but not destruction of the epithelial structures. In the regressive lesions under study, the infiltrations about the sweat glands are among those most strikingly reduced in extent. The ready infiltration of the coil glands in leprosy has always been attributed to their rich capillary bed. It is reasonable to attribute the ready regression of foci in these areas to the same factor.

Atrophy of the Corium.—The presence of infiltrative foci in the corium leads to much distortion and disarrangement of the coarse collagen fibres. Large nodular lesions compress many out of existence. When such lesions regress there is no evidence of any regeneration of collagen fibres. Rarely there is some proliferation of elastic tissue as described by Milasch,[3] seen in one of the present cases. More often the collagen fibres are simply atrophic, and the corium as a whole is thinned, or edematous in appearance. Often the collagen fibres stain peculiarly, retaining a little hematoxylin, and failing to take acid fuchsin. Rarely nuclear remnants are left behind in distorted areas. In three cases lipoids are deposited, some apparently within and between collagen fibres, without the presence of cells, and quite separate from the lipoid deposits associated with granulomas.

Persistence of Deeply Seated Foci.—The deeper foci, those infiltrating the subcutaneous tissue, usually invading discrete fat lobules, appear to undergo regressive changes much less readily than the superficial foci. Comparision of lesions indicates that the proportionately small number of deep foci in the bacterioscopically negative cases is due to their original absence, not to healing processes, which would leave some residue.

Just as activity in a chronic leprous lesion is usually more pronounced in the superficial areas, so also regressive changes

appear to take place here more readily. It might be said that the changes, whether progressive or regressive, seem to be more active nearer the surface of the skin. The importance of this is that lesions of lesser extent or duration, which have not so extensively infiltrated deeper parts of the skin, may be expected to respond to treatment, or to regress, better than others. Here again it is possible that the capillary blood supply is a determining factor. In several cases there are many bacilli in the deeper foci, and comparatively few in the superficial.

Table 1.

Epidermal Changes.

Character of Epidermis.	Number of Cases.
Papillae wholly flat ...	18
Papillae partly flat ...	8
Acanthotic	2
Normal	4

Table 2.

Distribution of Foci in Different Layers of the skin in 10 Positive and 10 Negative cases.

Site of Foci.	Bacteriscopy Pos.	Neg.
Superficial ...	5 –	3 –
Middle ...	6 –	2 –
Deep	6 –	1 –

Vascular Changes.—The author[4] called attention to the frequency and importance of bacillary infection of blood vessls in a majority of lepromatous lesions. These lesions with bacilli in endothelial cells provide a continuous source of organisms for further spread of the disease by way of the blood stream, and production of new lesions of hematogenous origin.

In the present cases no example of vascular infection has been encountered, with bacilli either in vessel walls or in endothelial cells. Lesions of vessels without bacilli are observed in seven cases. In these, cellular infiltration of the vessel wall indicates a vessel formerly infected. Venules and capillaries with large prominent endothelial cells are outspoken in many lesions.

In one case there is infiltration of the superficial vessels by neutrophilic granular leukocytes in a most striking manner. This is in a 40-year-old white woman with leprosy of 19 years' duration which has improved tremendously on promin therapy. Bacilli were found in a single focus in a single section of several searched, and nowhere in relation to the blood vessels.

Polymorphonuclear Neutrophilic Leukocytes. These cells are ordinarily absent from the chronic leprous granuloma, occurring only in the presence of ulceration, or in small numbers in acute reactive inflammatory phases, or from unrelated secondary processes.

In most of the regressive lesions they are also absent. However in seven cases, including the above with vascular infiltration, they are found, once in considerable numbers infiltrating all the granulomatous foci. In two cases these cells are observed invading large globi which seem to be undergoing disintegration. In no case is phagocytosis of bacilli by the granular leukocytes observed.

Lipoids. All lepromatous lesions and leprous granulations contain large quantities of lipoids. These are present in the vacuolated cells in the earliest lesions, even as in the epithelioid cells in tuberculosis, but in leprosy continue to increase in quantity with the chronicity of the lesion, making old solid lesions greasy in texture. The lipoids are mixtures of fatty materials including much neutral fat, but are free of cholesterin.

The lipoids persist beyond the life or activity of the leprous lesion. Leprous foci which appear totally obsolete are not scars, but collections of fat-laden cells. Many of these are vacuolated, and are of the same appearance as the original bacillus-containing cells.

It has often been suggested that the lipoids and waxes present in the bacillary body of the tubercle bacillus act as a barrier to the action of chemical or therapeutic agents, these organisms being possessed of a high resistance to chemical destruction. In the present studies obsolete bacillus-free cellular foci are as rich in lipoids as foci containing bacilli, and there is no question that bacilli are often removed from, or disappear from, the lesions in its presence. Thus it is not possible to argue from these studies that the cellular lipoid, presumably derived from the host, but possibly also from the bacilli, plays a role in experimental therapy. That it does play an important part in the histiogenesis of the lesion is another matter.

Fibrosis. Scarring is not a feature of the regressive leprous lesion. Intense scarring occurs in the healing of ulcerated lesions, but in the more common non-ulcerated lesion it is usually absent. In one case there is intercellular fibrosis in most of the foci, which is regarded as an accentuation of the usual connective tissue framework of the lepromatous granulation. In two cases there is similar fibrosis about sweat glands. A third case is one in which the previous biopsy showed a peculiarly large number of fibroblasts in the granulomas, which condition persists two years later, although most of the bacilli are gone.

Tubercle Formation. One of the questions raised in this study was whether regression of the disease might lead to reversion from

the lepromatous to the milder tuberculoid form of the disease, with histologic tubercle formation and only rare organisms. All the cases in this study were examples of mixed and lepromatous leprosy clinically. In two of the biopsies epithelioid cells are observed, and in one of these the distribution of foci suggests that the case might have possessed tuberculoid features at some time in the past. The previous biopsy in this case likewise shows epithelioid cells. Thus in these cases it is believed the traces of tuberculoid change must properly be attributed to an earlier process.

In a third case there are giant cell-epithelioid cell formations apparently of recent origin. Some are proliferations about disintegrating globi. Others are mixtures of epithelioid cells and foreign body type giant cells. However, these are small, and are embedded in lepromatous tissue of the usual sort. Thus, in none of the cases is there any suggestion of conversion to any other type of leprosy.

MODE OF ACTION OF PROMIN.

Daily intravenous injections of promin produce high but transitory blood levels. Clinical improvement is characterized by:

(1) Prevention, or healing, of secondary infection, especially of the upper respiratory tract, and of ulcers of the extremities.

(2) Elimination of the often severe acute reactions which are associated with exacerbation of the disease.

(3) Prevention of formation of new lesions.

These histologic studies suggest that promin effectively rids the blood vessels of bacilli. The bacteriostatic action of promin appears adequate to do this. There is little or no evidence that promin succeeds in destroying bacilli in the cells of the tissues. Most of the atrophic regressive changes seen in the tissues are also seen occasionally in cases which regress spontaneously, or in cases which improve spontaneously in the intervals between periods of activity, Leprosy has a certain tendency to be a self-limited disease, never destructive in character.

The long time required for promin treatment to show beneficial action, and the very slow eradication of organisms from the tissues, indicate that the genuine improvement under prolonged treatment stems from the eradication of vascular lesions, eliminating the dissemination of organisms by way of the blood stream, and preventing the development of new lesions of hematogenous origin. But the slow process of destruction of bacteria in tissue cells appears to occur at much the same rate as in the common periods of remission, which are a normal characteristic of most cases of

untreated leprosy. Certain unusual features, such as the persistence of deep foci, and the ready regression of infiltrations of sweat glands, suggest that a luxurius blood supply favours the regression of focal lesions.

The absence of acute reactions under promin treatment strongly suggests that blood stream dissemination of bacilli is essential for their production. In the absence of these acute reactions the lesions have a natural tendency to regress. There are, to be sure, exceptions. There are lesions with their bacilli which persist, even when other lesions in the same patient vanish. The persistence of some cellular reaction well beyond the disappearance of organisms in bacterioscopically negative lesions suggests that the criterion of presence or absence of demonstrable bacilli is not a wholly reliable indicator.

SUMMARY AND CONCLUSIONS.

Under promin treatment, the improvement in leprosy is not accompanied by characteristic cellular changes. Those which do occur are predominantly atrophic in character, with extremely slow and gradual lessening of numbers of organisms in the lesions to the point of final disappearance in 10 of 32 cases examined. These changes do not differ materially from similar changes occurring in spontaneous remission without treatment of any sort, or during interim periods of inactivity or regression between phases of acute activity.

The important finding is that promin appears to eliminate bacillary infection of the blood vessels and blood stream, thereby preventing the formation of new lesions. The atrophy of focal lesions is also more apparent in areas with a more generous blood supply. The results indicate strongly that the best results may be expected in those cases in which treatment is begun in a comparatively early stage of the disease.

A more powerful bactericidal agent than promin appears necessary for the chemical destruction of bacilli within tissue cells, and especially those within globi.

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CLASSIFICATION OF LEPROSY CASES.

E. MUIR.

The importance of a detailed and reliable method of classification and case-taking cannot be too much emphasised. Without this the progress of the disease cannot be correctly traced, and a true, continuous picture of its course arrived at. Also, now that more effective forms of treatment are becoming available, it is even more necessary to be able to estimate with precision the signs of gradual recovery.

It is equally important to be able to compare cases of diverse races and those living in different countries, or under dissimilar climatic, dietetic or social conditions. Without a precise and universally recognised system of typing and case-taking an accurate comparison is impossible.

There are six chief criteria by means of which cases of leprosy may be classified: Clinical, topographical (skin, nerves etc.), histopathological or structural, bacteriological, immunological (lepromin test), reactional.

PRIMARY CLASSIFICATION.

A clinical classification was originally used and, as far as it goes, this is the simplest and most convenient. But clinical aspects are so numerous, and often so confusing, that we require a more reliable basis of grouping, a final court of appeal when the clinical, topographical and even bacteriological findings leave us in doubt. The microscopic structure of the lesions gives us a standard which, though not always entirely satisfactory, is at least the best available.

What is known as the Panamerican Classification* divides leprosy primarily according to the histological picture into three types. In two of these types, the lepromatous and tuberculoid, the picture is characteristic and distinctive, but in the third it is uncharacteristic and indistinguishable from other chronic inflammatory conditions.

The microscopic structure thus provides a simple and reliable basis of primary classification. But it is only in a well-equipped laboratory and in the hands of a trained pathologist that this criterion can be applied, and these facilities are not available in the majority of cases.

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*Adopted at the Panamerican Conferenec held in Rio de Janeiro in October, 1946.

It is generally necessary therefore to use a combination of the other more easily available criteria, especially the clinical signs, bacteriological findings and, where possible, the lepromin test to find out the structural type to which the case belongs.

It is important, therefore, to discuss in turn the usual clinical, bacteriological and lepromin findings associated with each of the three structural types: lepromatous, tuberculoid and uncharacteristic.

(1) The structural picture of *leproma*, with its Virchow or foamy lepra cells surrounded by small round cell infiltration, is not confined to the skin or subcutaneous tissue; the same picture is found in the mucosa, nerves and internal organs.

The lepromatous case has in its advanced stages certain clinical appearances which mark it out from the other two types, namely diffuse thickening of the skin (especially of the face, arms and legs), nodulation, and loss of supercilliary hair.

In early cases the clinical appearance is less distinctive, but the nature of macules, their shape, size, number and distribution, and especially their central thickening and absence of a raised or incisive margin, are at least an indication of the lepromatous type, Nerve thickening is not nearly as marked as in the tuberculoid.

The bacteriological smears are most important. Globi are characteristic of this type, and a case with many bacilli is almost certainly lepromatous unless it be a reacting tuberculoid, when the clinical peculiarities and the lepromin test will, as a rule, give a clear distinction. The lepromin test is invariably negative.

Acute reaction is generally much more severe in the lepromatous than in the tuberculoid type, and this is natural considering the infinitely greater number of bacilli present.

(2) The *tuberculoid* structure, with its denser cellular formation in the shape of follicles or cords with clear-cut edges, and with its epithelioid and giant cells surrounded by round cell infiltration, is found in the skin and peripheral nerves alike.

Clinically, the most typical skin lesions (leprides) show a tessilated appearance, due to small tubercles one or two milimetres in size, which stand out from the skin surface especially at the advancing margin, but coalesce and often flatten out in the older and more central part of the lesion. The tubercles correspond with the cellular cords which press on and cause projection of the epithelium.

The peripheral nerves are most affected in the tuberculoid type and may be markedly thickened and tender; they sometimes even caseate and form abscesses. There is in consequence a greater

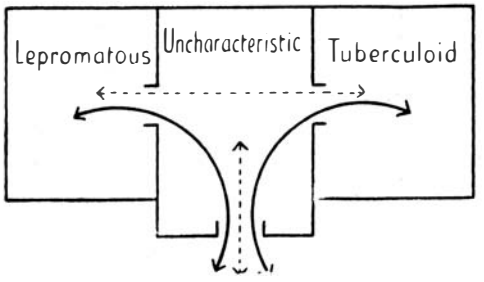
degree of anaesthesia, and the distal parts of the limbs suffer more from trophic and sensory changes.

When lesions are in acute reaction a few or more bacilli may be easily found, but they often disappear as the reaction subsides. Otherwise bacilli are few and hard to find.

The lepromin test is almost always positive, generally giving a fairly strong reaction.

(3) Unlike the first two types which are sometimes described as " polar " because of their strongly divergent signs, the third type does not show a characteristic histological picture. There are neither foamy Virchow cells, nor yet epithelioid and giant cells, only the small cell infiltration common to the other two types and to most chronic inflammations. It has therefore been called " uncharacteristic."

Uncharacteristic cases may be *static*, remaining in this type throughout the course of the disease and never passing on into another type, till perhaps in the end they recover. Or they may be in one out of three forms of transition: (a) *initial*, in the course of passing on into the tuberculoid or the lepromatous type; (b) *intermediate*, passing from one of the characteristic types into the other, or (c) *vestigial*, passing out of one of the characteristic types on the way towards recovery. In initial cases, it may be compared to the entrance hall of a house (see diagram) with doors opening to the right (tuberculoid) or to the left (lepromatous). This is the hall of anergy. If effective allergic response comes in time before the bacilli are too many, the case enters to the right (tuberculoid); failing this it may gradually drift to the left (lepromatous) as there is no effective check to bacillary multiplication.



But in the actual classification of a case at any one time we are not concerned with change and transition. We have to dot his present position, though a series of such dots made at subsequent examinations may indicate the curve he has followed, or chart his course in the house of classification.

The chief indication of an uncharacteristic case is one of exclusion, its failure to belong to either of the other two types.

Clinically the lesions are large or small, reddish or whitish (or a combination of the two) in comparision with the surrounding skin, flat and thin when picked up between the finger and thumb, and without the thickened leproma or nodule of the first type or the outstanding and thickened tubercle-formation of the second.

Initial lesions are generally limited in size and require a good light to recognise them. They would often be missed were it not that knowledge of leprous relatives or other contacts has led to careful examination. Changes in sensation are slight as a rule and require careful testing. Such lesions may disappear, to be followed later by a more serious form of the disease.

Residual lesions on the other hand are often more extensive and more easily recognised. Anaesthesia is more marked and there may be definite polyneuritic signs in the extremities and the face, and thickening and tenderness of the nerves.

Bacteria are nil or few in number, and the lepromin test varies from negative to moderately positive.

Unlike the other two types, the uncharacteristic one seldom, if ever, shows a reactionary phase; when reaction does occur it is generally a sign that the case has passed on into one of the two polar types.

Regarding transition from the *one polar type to the other*, there is a difference of opinion, Some hold that the tuberculoid is never transformed into the lepromatous, others that it is not an infrequent occurrence. This is a matter which requires further investigation. There seems little doubt that leprosy varies considerably in different countries, or even in different parts of one country, and this may, at least in part, account for the divergence of view.

The writer's opinion is that this phenomenon does undoubtedly occur, in fact there are many cases in which this has been checked up histologically, clinically, and by the lepromin test. It is not uncommon to find an advanced lepromatous case with one or more circular limited patches which mark the site of former definite tuberculoid lesions, and which still maintain their resistance to invasion from the surrounding lepromatous skin.

Passage from lepromatous to tuberculoid is more doubtful, as would be expected. Definite lepromatous cases not infrequently become arrested in the sense of becoming and remaining bacteriologically negative as far as careful routine examination is concerned; but it is a less common occurrence for such a case to devolop a strong or even moderately positive lepromin test, such as would be expected if it were transformed into a tuberculoid. Whether this

(transformation into tuberculoid type with positive lepromin test) will occur in future under treatment with sulphones remains to be seen. Certainly such a transformation in the course of recovery would prognostically be of great value, as showing that the natural resistance of the body to leprosy had increased.

SECONDARY CLASSIFICATION.

It is important after making the primary or basal structural classification with the help of the other criteria, to pass on to secondary classifications, so as to describe the case in greater detail.

Clinical and Topographical. In sub-classification we consider first the various organs affected: skin and subcutaneous tissue, mucosa of nose, mouth and throat, the nerves and polyneuritic changes, the internal organs, etc.

The following is a brief list of points to be noted in making a clinical examination:—

(1) *Skin lesions* are as a rule the most important, whatever the primary type. Macules and leprides should be described as to their number, size and distribution; their colour, thickness, centre and margin; the presence of tubercles, keratosis and changed superficial markings; loss of hair and sweat function.

Diffuse lesions should be delineated, giving their extent and the changes from the normal as above; and the presence, size and number of nodules should be specified. Lesions of the subcutaneous tissue should be mentioned.

(2) *Mucous membranes* affected, of nose, mouth, throat, air passages, should be described.

(3) *Nerves.* An account should be given of tenderness, thickening, nodulation, caseation or abscess formation of peripheral nerves, and of secondary, trophic and sensory changes in the hands, feet and face.

(4) *Internal Organs* are often affected, but clinical signs such as enlargement of the liver and spleen are seldom apparent. Atrophy of the testicles, followed by gynecomastia, is a not uncommon occurrence in advanced lepromatous cases.

(5) Of the *special sense organs,* apart from those of the skin, the eye is the most seriously affected. Careful examinations, if necessary with the use of atropine, should be made for early signs of conjunctivitis, keratitis and irido-cyclitis. In tuberculoid and uncharacteristic cases,

lagophthalmia and consequent changes in the eye-ball and adnexa should be kept in mind.

In all clinical examinations the presence and degree of reactive signs, whether chronic, subacute or acute, should be noted.

Bacteriological Examination. It is necessary to note not only whether a case is bacteriologically positive or not, but also the degree of positivity; whether there are globi, single bacilli or peculiarities in staining. The distribution of areas found positive should be noted, in the nose, in clinically apparent skin lesions or in seemingly normal skin. Such details are of increasing importance, not only because they distinguish lepromatous from reacting tuberculoid cases, but because in the new and more effective forms of treatment the chief criterion of improvement is bacteriological rather than clinical.

Lepromin Test. In one sense this test is the most important of the criteria available for the practical classification of leprosy. More than anything else it indicates the power of the tissues to react to and destroy the lepra bacillus.

The results of the test vary in three respects:

(a) Variation according to the type of case and the individual.

(b) From time to time the degree of positivity varies in the same case. It should therefore be repeated frequently, if possible every three months.

(c) There may be a distinct difference in the degree of reaction inside and outside of a skin lesion at any one time.

For the sake of both primary and secondary classification it is important that the lepromin test be done accurately. For this it is necessary to have a standard antigen, and a standard method of reading results. These standards should be fixed by an accepted authority, such as an international congress.

A standardised test would make it possible to compare cases all over the world, and might also be of great value in confirming recovery if lepromatous cases under new forms of treatment were found to develop a positive result.

Case-Taking.

In taking a case a great many details may be gathered under the descriptions suggested above, and especially under the clinical definitions.

For practical purposes, however, I propose the use of three tabular forms, the first being of a general nature, the second describing circular skin lesions, and the third dealing with nodules,

FORM 1.

	Skin and Mucosa.				*Nerves and Polyneuritic.*				*Bact.*				*Lepromin.*				*Reaction.*			
	-	+	++	+++	-	+	++	+++	-	+	++	+++	-	+	++	+++	-	+	++	+++
Lep																				
Un																				
Tub																				

ulcers and the nose and eyes. These include the main elements in the classification, but they can, if so desired, be elaborated in further detail elsewhere in the patient's chart.

In Form 1 the three primary types are given in longitudinal columns. The first two vertical columns are clinical, giving the degree of affection of skin and mucosa, and nerves and polyneuritic lesions, while the other three deal with bacteriological examination, lepromin test and reaction. Each vertical column is subdivided into four for negative, and one, two and three plus.

In the first column, negative would mean that there were no lesions of the skin and mucous membranes of nose, mouth, etc. One plus = lesions covering in aggregate not more than 150 sq. cm. (25 sq. inches), two plus covering up to one quarter of the body surface, and three plus more than that area.

In the second column, one plus indicates thickening and tenderness of one or two nerves without trophic changes in hands, feet or face; two plus means involvement of more than two nerves and/or trophic changes of the face or one hand or one foot; three plus indicates more extensive neural or trophic involvement.

In the bacteriological column one plus indicates bacilli present, but no globi and not more than 10 bacilli in any one field of a smear taken by biopsy from nose or skin by the ordinary routine method. Two plus indicates one or more globi and/or more than 10 bacilli in any one field. Three plus indicates more than ten globi in the whole of any ordinary skin or nasal smear.

In the lepromin column, one plus indicates in the immediate reading a flare up to 5 mm. diameter and/or in the delayed reading a nodule up to the same diameter; two plus up to 7 mm. in early flare and/or delayed nodule, but without tissue distruction at the centre; three plus more than 7 mm. and/or tissue destruction at the centre.

In the reaction column, minus indicates no reddening or local swelling or thickening of the skin or mucosa, and no thickening or tenderness of a nerve. One plus would indicate one or more erythematous macules or other lesions without anything of the nature of a flare up, and/or thickening and tenderness of minor degree in nerves. Two plus indicates lepra reaction of moderate degree in either lepromatous or tuberculoid type. Three plus means a severe reaction with considerable swelling of lesions, fever and/or liquifaction of lesions and, in tuberculoid cases, severe and painful swelling of leprides and/or nerves.

FORM II.

Circular Skin Lesions.

1. Number −, 1 to 10 or 10+.
2. Area index in sq. cm.
3. Area central flattening in sq. cm.
4. Margin breadth in cm.
5. Margin serration − to +++.
6. Hypopigmentation + or −.
7. Anaesthesia − to +++.
8. Analgesia + or −.

Form II deals with more or less circular, circumscribed lesions such as macules and leprides which need more detailed description than is given in Form I. The following eight points should be noted.

1. Number of discrete lesions, viz. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, and 10+ when more than 10.
2. Area index. This is arrived at by measuring in centimetres ($2\frac{1}{2}$ to 1 inch) the greatest diameter of the largest discrete circular lesion, and multiplying it by the length of the diameter at right angles. If no discrete skin lesions, mark '−'.
3. Area of central flattening. Here again take the largest discrete lesion, and, if there is a flattened area in the centre, measure its size in the same way, otherwise mark '−'.
4. Margin breadth. When there is a flattened centre measure the breadth of the margin in cm.; otherwise mark '−'.
5. Margin serration. Serration of the edge is one of the clearest signs of activity and spread. Mark the degree of serration negative or one to three plus.
6. Colour changes. Hypopigmentation is due to loss of pigment, to be marked + or −. Reddening is due to reaction and is marked in Table I.
7. Anaesthesia to light touch, as tested with a feather. Ask the blind-folded patient to place his finger on the points touched. This can be graded from − to +++ by using three grades of touching instrument.
8. Analgesia. This can be tested by the two pin method. A healthy and a suspected area being pricked simultaneously, and the patient asked each time which he feels most.

FORM III.

Nodules −, 1 to 10 or 10 +.

Ulcers. Nodular −, 1 to 10 or 10 +.
Trophic −, 1 to 10 or 10 +.

Nose condition:		R. −, +, + +, + + +.
		L. −, +, + +, + + +.
Eye.	Lepromatous.	R. −, +, + +, + + +.
		L. −, +, + +, + + +.
Eye.	Trophic.	R. −, +, + +, + + +.
		L. −, +, + +, + + +.

In Form III other details are given:— the number of nodules, and of lepromatous or trophic ulcers, the condition of the nose, and lepromatous or trophic eye changes.

In the nose condition + indicates infection without nodulation, + + nodulation, partial blocking, but no ulcers, + + + ulceration and blocking.

In lepromatous eyes + means conjunctival affection with punctate keratitis, or slight ground-glass appearance spreading from the limbus, and/or pupil irregular but free; + + = nodulation of the cornea and/or fixed pupil; + + + = vision destroyed.

In trophic eye conditions + = lagophthalmia, + + = ulceration of cornea or scars of former ulceration, + + + = vision destroyed.

SUMMARY.

1. A classification of leprosy, following that adopted by the Panamerican Conference in Brazil, is explained and expanded.

2. Primarily there are three types: lepromatous, tuberculoid and uncharacteristic, based on the histological picture, but usually indicated by clinical, bacterioscopic and lepromin findings.

3. Subclassification gives further clinical, topical, bacteriological and lepromin details.

4. A simple method of case-taking in three tabular forms is suggested.

REVIEWS.

International Journal of Leprosy, Vol. 15, No. 1. Jan.-March 1947.

Chemotherapy of Leprosy, by G. H. Faget. This article describes with clarity and conciseness the technique and administration, the therapeutic and bacteriological effects and the results of treatment by promin, promizole and diasone. The author claims that the results he describes merit the claim that sulphones have a progressive and specific action in leprosy. The article in general has perhaps a tendency to understress the difficulties, dangers and limitations of sulphone therapy but it can be recommended as an excellent short summary of the present chemotherapeutic position.

Injury of Nerve Elements of the Tongue Root in Lepromatous Leprosy, by N. E. Ermakova. This is a more or less preparatory article containing a careful and well illustrated study of leprotic invasion of the tongue. The author traces the spread of bacilli in the gustatory goblets and along the perineural sheaths suggesting that the flow of lymph in the nerve sheath is the medium whereby infection is extended.

A Study of the Bacilli Tissue Cultures of Lepromata in Serum Media, by John H. Hanks. The author summarises as follows:—

"1. Tissue cultures from four lepromata were grown and maintained in a viable condition in serum media for period of from 14 to 34 days.

2. The infected macrophages died early in the history of the cultures and deposited their bacilli within the necrotic mass of the original explants.

3. The only cells that persisted throughout the life of the cultures were fibroblasts, which ordinarily contained no bacilli or only a few.

4. Quantitative rating of the explants with respect to their bacterial content did not reveal an increase in the total mass of bacilli.

5. The development of turbidity in the plasma of older cultures was found not to be attributable to multiplication of bacilli in this site as claimed by earlier workers."

The Fate of Leprosy Bacilli in Fibroblasts cultivataed from Macular and Tuberculoid Lesions, by John H. Hanks. The author summarises as follows:—

"1. Cultivation and maintenance of the fibroblasts from macular or tuberculoid lesions for periods of two to seven months did not provide for multiplication of leprosy bacilli within these cells.

2. The total numbers of intracellular bacilli, or the proportion of cells with bacilli, sometimes increased during intervals as long as three months, but this rise was always followed by a decline in bacilli and by signs of their disintegration.

3. Evidence is presented that the concentration of bacilli in the outgrowing cells was influenced by early and transient or delayed or discontinuous transportation of micro-organisms from the primary explants of the lesions, and also by the degree to which the bacilli were divided among the growing cells.

4. Pigment granules, as well as bacilli, occurred in the fibroblasts from the papillary layer of skin. Their incidence was controlled by the factors which determine the occurrence of bacilli, and they were usually

to be found in the cells which contained bacilli for the longest intervals. These inert particles served to identify such cells as containing material from the original explants.

5. The fibroblasts from these clinically more resistant forms of leprosy were found capable of rapidly destroying the micro-organisms. This capacity in accordance with the numbers of bacilli phagocyted and with the physiological activity of the cells."

The Fate of Leprosy Bacilli in Fibroblasts cultivated from Lepromatous Lesions, by John H. Hanks. The author summarises as follows:—

"1. Fibroblasts from human lepromata were maintained *in vitro* for intervals of 7 to 14 weeks. Irrespective of whether the new growth was left attached to the original explants or was subcultured in successive series of tubes, the proportion of cells containing bacilli (and the content per cell) decreased continuously.

2. By the use of carbon from India ink as inert control particles, all the quantative relationships between the bacilli and the cells were duplicated, except that the bacilli disappeared more rapidly than the carbon.

3. The bacterial and carbon content of young cultures were found to depend on the concentration of particles and cells in the explants and on the luxuriance of early outgrowth, while the concentrations of particles in older cultures of comparable early histories was related inversely to the degree of cell growth.

4. A temperature of 34 degrees C., slow growth, low cell metabolism, and a slightly alkaline medium permitted maintaining bacilli in the cells in apparently good condition for long intervals, but did not prevent an eventual inversion of the bacillus-carbon ratios. More active cell metabolism, or a lower ph, accelerated the disappearance of the bacilli. Analogous differences in physological conditions differentiate the group of peripheral tissues in which leprous lesions are common from the internal organs in which the bacilli are rare or of abnormal appearance."

There are two further short articles by the same author on the influence of carbon particles in rat leprosy and the meaning of plasma turbidity in the plasma of tissue cultivation.

The same author also contributes *Attempts to infect Chick Embryos and Chick Tissue Cultures with Bacilli from Human Lepromatous Lesions.* He summarises as follows:—

"Bacilli from leprous nodules were used to infect developing chick embryos, tissue cultures from chick embryos, and newly hatched chicks.

There was no evidence that the micro-organisms grew during the brief interval between the injection of bacilli into chick embryos and the hatching of chicks.

When the bacilli were injected into chick tissues prior to the preparation of explants for cultivation, the bacilli occurred almost exclusively in the macrophages during the existence of these cells and only later in the more persistent fibroblasts. The bacilli appeared to be no more toxic than carbon particles. Either kind of particles stimulated the cells enough to hasten the digestion of the plasma and to reduce measurably their longevity during continuous growth in non-renewed media. The bacilli within cells disintegrated more rapidly than those outside."

Nothing could have been more timely or apposite than the Editorial of this number of the International Journal of Leprosy. It calls in no uncertain terms for a planned and co-ordinated scientific study of the sulphones. The warning comes none too soon for already there is a marked absence of the use of controls

with adequate doses of hydnocarpus oil in the recorded description of sulphone therapy.

The number also contains a full report on the Second Pan-American Leprosy Conference held at Rio de Janeiro, 19th-27th October, 1946. The reports of the Sub-committees on Classification, Epidemiology and Treatment are given in detail.

A short article, *High Lights of Wartime Culion*, by Dr. Wade, gives something of the story of the world's largest leper settlement under Japanese occupation. There is much to be read between the lines and the story is told with a terse and grim objectivity that makes compelling reading.

Leprosy in India, Vol. XIX. No. 1. January 1947.

The Editorial of this number is a very carefully considered survey of the present position with regard to the classification of leprosy. In particular there is criticism of the proposed uncharacteristic grouping representing "a collection of heterogenous types differing in clinical immunological and histological findings and in prognosis."

The Lepromin Reaction in Subsided Lepromatous Cases, by Dharmendra and N. Mukherji. This is a study of the lepromin reaction in seventeen lepromatous cases which became clinically arrested and bacteriologically negative. The study is a detailed one and should be read in full. The authors conclude that improvement in lepromtous cases is seldom accompanied by a change to a positive lepromin reaction although a slight sub-positive increase in reaction is often observed. Where there is a tendency to relapse the sub-positive response is seldom found.

Legislation in Leprosy in India, by J. J. Joseph. This article is a plea for modern leprosy legislation on an all-India basis. There is a preliminary discussion on why leprosy disappeared from the British Isles which contains two ingenious and new theories. One is that the lazar houses were plundered and destroyed by ravaging soldiers in internal wars. The other is that during Britain's period of colonisation in the 17th and 18th centuries the lepers emigrated. These theories have the merit of naïvety but the author demands our respect in his call for new and enlightened legislation for India.

Dr. Dharmendra and Dr. S. S. Jaikaria contribute a short but important article *Failure to Sensitize Presumably Non-leprous Individuals to Lepromin.* The authors describe an experiment

whereby they find that lepromin test readings in non-leprous persons are not affected by the repetition of the test.

Promizole Treatment of Leprosy. A Preliminary Report, by G. H. Faget, R. C. Pogge and F. A. Johnson is a reprinted article of a detailed study of seven cases which have received Promizole treatment for at least a year in doses up to 6 gm. daily. The authors feel that results may be more rapidly obtained with Promizole than with either Promin or Diasone.

The attention of readers is drawn to the article on Leprosy by Dr. Lowe in *Principles and Practice of Tropical Medicine* by L. E. Napier. The article on leprosy in the text book covers some forty pages and is the most succinct and able resume of its size that we have yet encountered. It is to be recommended to all who, unable to study the larger text books or detailed literature of the disease, wish for a compact and authoritative study of leprosy.

Stein, A. A., and Dorofejew, W. N. Zur Frage de Klinik und pathologischen Anatomie leproser Iritis. Int. J. Leprosy, 1945, **13,** 43-66. (Dec.).

The character and certain peculiarities of ocular leprosy affecting the uveal tract are discussed by Stein and Dorofejew. The total number of cases examined was 298, of which 264 were of the lepromatous or mixed form and 34 of the neural form. In the lepromatous group there were 92 cases of chronic iritis and iridocyclitis. In 145 patients there were various symptoms of involvement of the iris. In the neural group there were 5 cases of iritis.

The three most important forms of leprous uveitis are those with miliary lepromata, those with a solitary leproma, and diffuse parenchymatous iritis.

In the pathological investigation of 27 fragments of iris, the authors found that 8 specimens showed seroplastic iritis, 16 specimens showed seroplastic iritis with miliary lepromata and in 3 specimens there were no specific changes.

In the seroplastic group the structure of the iris is fairly seriously affected. The stroma is very dense and in most cases the iris is very thickened. The sphincter and dilator muscles cannot be recognised. There is considerable lymphocytic infiltration, but few blood vessels compared with normal irides are found. The layer of pigmented epithelium is undamaged and is absent in only a few spots on the iris. On the anterior surface of the iris there are many branched cells containing many granules of brown pigment. Leprosy bacilli in rounded clumps are present in large

numbers, but most of the bacilli are in an abnormal state and do not stain evenly. There are many red acid-fast granules. In this group there are merely signs of chronic inflammation, without formation of the typical leprous granuloma. The process is accompanied by proliferation of the stroma, abnormality in the distribution of the pigment, disappearance of the muscle bundles, and the presence of a rather large number of leprosy bacilli. Virchow's lepra cells are not seen.

In the seroplastic iritis with clinically observed miliary lepromata group the structure is different. The iris is still more severely affected, the thickening more pronounced and there are local prominent swellings. The stroma is denser than usual, is poor in blood vessels, is infiltrated by a considerable number of lymphocytes, and the sphincter and dilator muscles are unrecognisable. The pigmentary layer is damaged, being absent in some places and very thin in others. In the anterior part of the iris there are fairly numerous cells with granules of brown pigment and in places accumulation of large cells with a rather pale, large, oval nucleus, i.e., histiocytes. Numerous yellow accumulations of granular lipoids are revealed after staining with Sudan III and in some cases the lipoids show vacuoles bounded by a rim of brownish colour. The walls of the few blood vessels are much thickened and the lumen may be narrowed or occluded. Staining for lepra bacilli reveals a colossal number of these. They appear scattered through the iris or in globular groups containing histiocytes. Most of the bacilli are abnormal; they take stain badly, there are shortened forms and granules. Very often the staining is so faint that one can only speak of bacillary shadows. In this group, beside the changes observed in plastic iritis, there are the histiological findings typical of lepromatous leprosy, which are very small, circumscribed granulomata of specific structure with lepra cells containing lipoids, vacuoles and large numbers of leprosy bacilli.

In the third group of three specimens, in which clinical and histological examination did not show any inflammation, there was one case in which lepra bacilli were found. All three cases belonged to the neural type of leprosy.

The pathological findings agree with the clinical findings. If the corneal microscope revealed miliary lepromata, they were also seen on histological examination, and when plastic iritis was diagnosed, histological examination showed only non-specific chronic inflammation together with leprosy bacilli. Both forms are undoubtedly part of the leprous process. Plastic iritis alone was was found to occur in patients with leprosy of long duration, in which the process is becoming extinct, with extensive atrophy and

cutaneous scars, or in patients with a mild form of the disease, with few lepromata and infiltration.

On the other hand, progressive leprosy with numerous cutaneous lesions is associated with iritis and miliary lepromata. The reaction of the iris is thus a guide to the state of immunity of the patient.

E. O'G. KIRWAN.

MEMORANDUM ON THE INTERNATIONAL CONGRESS OF LEPROSY

TO BE HELD AT HAVANA, CUBA, IN APRIL, 1948.

The next International Leprosy Congress will be held in the Spring of 1948, and an invitation has been received and accepted from the Government of Cuba to make Havana, Cuba, the location of the Congress, the date being fixed as April 3-11, 1948.

The Government of Cuba is issuing official invitations to all Governments with which they have diplomatic relations, asking them to send official delegates, and these will be delivered in due course.

All members of the International Leprosy Association are also invited to attend, and those who can do so should notify the Secretary of the International Leprosy Association, 167 Victoria Street, London, S.W.1 as soon as possible. They should also notify the Secretary of the Organising Committee (Dr. Ismael Ferrer, Ministerio de Salubridad y Assistencia Social, Marianas, Habana, Cuba) of intention to attend, and of the manner and time of arrival.

Official delegates and members of the Association (whether they can attend or not) are invited to send in papers. These should be of such length that they can be read in ten minutes, and should deal with the subjects to be discussed at the Congress as maintained below. Titles and, if possible, short abstracts, of papers should be sent to the Secretary of the I.L.A. so as to reach him before the end of December, 1947. Copies of the papers themselves should be sent to the Secretary of the Congress so as to reach him before April 1st, 1948, or alternatively be delivered personally to the Secretary before the beginning of the Congress.

Leprosy will be discussed under the following five headings:— (a) Epidemiology and control, (b) Pathology and bacteriology, (c) Classification, (d) Therapeutics, (e) Sociology.