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CONTENTS

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EDITORIAL

As a result of the work of leprologists in many parts of the world, particularly Fernandez, de Souza Campos, Rotberg and Bechelli, followed by Chaussinand, Lowe and Dharmendra, to name but a few, a great deal of interest has been created in the possibility of giving protection from leprosy by means of B.C.G. vaccination. We, therefore, felt it was opportune to ask a well known worker in tuberculosis to give us a summary of his views on B.C.G. Vaccination and Immunity in Tuberculosis. In this number of the Review Dr. F. R. G. Heaf, Davies Professor of Tuberculosis in the University of Wales, has kindly contributed an article which will be of great value to workers in their studies of the relationship between B.C.G. Vaccination and the Lepromin Reaction.

There are several points of relevance in this article in connection with the question of the assumed protection of children against leprosy by the use of B.C.G. Vaccination. We would draw attention to certain statements of Prof. Heaf in order that leprosy workers may not be tempted to be over-optimistic in regard to the expression of their opinions in this matter. Prof. Heaf mentions that " we must not assume that vaccinated individuals can withstand large doses of virulent (tubercle) bacilli." This is consistent with Dr. Lowe's remarks in his article in the previous number of the Review, when he says " It should be made quite clear to everyone concerned that B.C.G. vaccination of those exposed to infection does not remove the necessity for taking every possible step to prevent or minimize contact between the open case of leprosy and healthy persons, particularly children." Wishful thinking may be a pleasant habit, but at least in leprosy it may retard rather than advance progress. We are reaching a stage in the campaign against leprosy when more certain victory is in sight, but let us remember that all these stimulating and heartening discoveries are merely skirmishes in this centuries-long conflict, and that the final clash with the enemy has still to be fought.

Some of the difficulties in evaluating the results of the tuberculin test in relation to B.C.G. described by Prof. Heaf are a timely reminder to those who contemplate embarking on this complicated investigation in leprosy, for they must be fully aware of all the possible errors when they come to assess their results. It cannot be too strongly emphasised, to use Prof. Heaf's phrase, that " the tuberculin test is a measure of skin sensitivity, and that it is quite

certain that tuberculin sensitivity and immunity are different entities, although there is a relationship between them." Let us therefore not too readily assume that B.C.G. vaccination gives immunity to leprosy, but go no further at present than Dr. Lowe does and conclude that it increases tissue sensitivity to the M. leprae, and therefore gives the defences of the body a better chance of overcoming the infection, or if leprosy develops, of showing the milder self-limiting form of the disease. We must, however, not forget that a person who is hypersensitive to lepromin, if he contracts leprosy, may become an active and gross major tuberculoid case, with all the possibility of serious residual deformity resulting from the excessive tissue reaction in the nerves. A markedly strong positive lepromin reaction may therefore be a mixed blessing. All these factors must be considered in any discussion with reference to the possible protection of B.C.G. vaccination in leprosy.

The story of Kuluva describes a most interesting co-operative effort between mission, Government and the African local administration, leading to what appears to be a successful experiment in the control of leprosy in part of Uganda. It is of interest to note that Dr. Williams favours the parenteral administration of the parent sulphone, and has devised a method of overcoming, not only the difficulty of making an aqueous suspension of D.D.S., but of reducing the time in giving injections to such a degree that he states, in justification of this method, that " by attention to technique a great deal of time otherwise spent in counting out and dispensing tablets could be saved." Certainly, at Kuluva, the organisation is such that it would be of interest if this method were given a wider trial. As yet the work appears not to have continued long enough for the assessment of bacteriological results, but we would consider the dosage of D.D.S. given to be on the low side. It might be of value if a comparison of the use of a suspension of D.D.S. were made with aqueous sulphetrone. The preparation of aqueous sulphetrone would be less time consuming, and would do away with what is after all a practical expedient, but we hardly think that this method would be altogether approved by our friends the pharmacists. We hazard the opinion that the equivalent of two grammes of sulphetrone, one gramme twice a week, would give as good results. We commend this article to the serious attention of those who may be of the opinion that the oral administration of Dapsone is not without its disadvantages.

An Evaluation of New Treatments, by Dr. W. S. Davidson reminds us of the care that has to be taken in assessing results. We

are interested in his claim of the apparent superiority of thiosemicarbazone, for we ourselves have come to the conclusion that this drug is not superior to the sulphones, and its daily administration and possible toxic side effects preclude it being used as the drug of choice in the therapy of leprosy. We look forward to further contributions from workers in Western Australia along these lines.

Dr. Mario Guadagnini's article on Lepromatous Nerve Lesions emphasises once again the importance of measures to prevent deformity arising in leprosy. This article stresses the need for operative interference at the appropriate time and, read in relation to Mr. Brand's work in S. India, will add further to our knowledge of the causation of these lesions. We have never been able to persuade ourselves that it is sound surgical practice to transpose the ulnar nerve in front of the internal condyle, for we feel that in such a position it is exposed to a greater degree of trauma, and that the simpler operation of resection of the sheath is as satisfactory. We will welcome views of workers who have had experience in these surgical procedures.

Sulphone Cilag is a monosubstituted sulphone, and as such is of considerable interest. The results of a limited experiment in treatment with this derivative are reported by Dr. K. Ramanujam, of Madras. His contribution will be read with interest. The general level of dose of the sulphones is much lower than originally thought, and this is no exception with this derivative. Sulphone Cilag is active as all sulphones appear to be, and therefore can be recommended for use, but it is hardly likely to replace the more economic parent sulphone or parenteral sulphetrone.

Dr. Corcos' article on the possible effect of sunlight on M. leprae will create considerable interest, and we look forward to his further investigations. The question of being able to decide as to whether a given smear of M. leprae contains live or dead bacilli is an important one, and any light on this matter is always welcome.

B.C.G. AND IMMUNITY

F. R. G. HEAF, M.D., F.R.C.P.

When a normal body is infected by tubercle bacilli, the tissues at the site of invasion immediately respond in a manner adopted towards any foreign body. There is a slight inflammatory reaction at the site of invasion. The bacilli are confronted at first with little resistance and therefore multiply rapidly and are carried by the lymphatics to the nearest

definite and after two weeks there is an increasing effort to suppress the multiplication of the bacilli. Phagocytosis becomes more active and an increase in the number of monocytes and grouping of endothelial cells is evident. At the same time there is an attempt to restrict the wanderings of the bacilli and localize the lesion. If the invading bacilli are in great numbers, or of sufficient virulence, this resistance of the tissues will be only partially successful and a further dissemination of the organisms to other tissues will take place, but the effort upon the part of the host to localize the lesion will continue wherever the bacilli may lodge. If, on the other hand, the number of bacilli is small, or the virulence is low, the complete isolation of the majority may take place along with the killing off of those that have escaped to other tissues. Most of the bacilli imprisoned in phagocytes will die and the increase in fibroblasts will tend to limit the lesion, although necrosis and caseation will be seen within the fibrous encirclement.

The power to produce this sensitivity to tubercle bacilli or tuberculo-protein is not possessed only by the living organism. Some degree of tuberculin sensitivity can be produced by phenol-killed tubercle bacilli, but it is slight and transitory. Dubos (1953)[1] has recently shown that such bacilli, when injected into mice, confer a certain degree of immunity as measured by the number of bacilli in the lungs following an injection of virulent tubercle bacilli. In mice, the degree of immunity produced by injecting non-heat-killed bacilli was similar to that following very small injections of virulent living bacilli. If immunity is measured by the speed of multiplication of the bacillus in the tissues, then non-heat-killed bacilli, attenuated and virulent ones can be said to produce similar degrees of immunity if the dose is regulated in each case. The attenuated organism is the one most satisfactory to use for this purpose and the strain prepared by Calmette and Guérin and known as B.C.G. is the one most frequently used, as it is harmless to man.

Suspensions of B.C.G. injected intradermally, or given by mouth, cause tuberculin sensitivity to develop in the vast majority

of individuals within six weeks. In infants it may take longer. A few individuals fail to respond to the injection and remain persistently insensitive to tuberculin. It is not easy to determine the duration of the tuberculin sensitivity produced, as any natural infection by tubercle bacilli following the injection will boost up the sensitivity. So for accurate observations on the point, complete protection from invasion by virulent tubercle bacilli is necessary. When this is made it is found that some individuals lose their sensitivity within twelve months of being B.C.G. vaccinated; others maintain it for as long as five or even seven years.

Although knowledge of the duration of tuberculin sensitivity following vaccination is of considerable value, a matter of greater importance is the degree of immunity against tuberculosis conferred by the vaccine. This can be measured by noting the incidence of the disease in vaccinated and unvaccinated comparable groups who are exposed to the same risk. This is very difficult to do and it is doubtful if a controlled trial can be organised that would be free of criticism when dealing with such a multifactorial disease like tuberculosis. Trials have been made and some are still proceeding by which it is hoped to assess the value of B.C.G. vaccination. Another method of assessing the degree of immunity conferred by the vaccine has been used by Dubos (1953)[2][3] who measured the number of bacilli in the lungs of B.C.G. vaccinated mice two weeks after they had been given injections of virulent tubercle bacilli. It was found that in the unvaccinated controls the number was 200 times as great as in the vaccinated animals. Although there is at present no scientific proof that B.C.G. vaccination confers on man immunity against contracting tuberculosis, there is strong presumptive evidence from observations that have been made in different parts of the world. That the protection afforded by B.C.G. vaccination against tuberculosis is only partial is easily appreciated by noting that persons who have been vaccinated do sometimes develop active lesions, even within a year or two of vaccination. These cases can be found in any country where B.C.G. vaccination is practised.

Among the numerous papers that have been published on the subject those of Hertzberg (1949)[4] Wallgren (1945)[5] Ferguson (1946)[6] Aronson and Palmer (1946)[7] Wilson (1947)[8] Myers (1952)[9] Levine (1952)[10] Irvine (1949)[11] van Deinse (1951)[12] Holm (1946)[13] and Palmer (1952)[14] are all of great value and should be studied. Some recent observations by Dahlstrom and Difs (1951)[15] are worthy of particular mention. They found that the incidence of primary tuberculosis in over 60,000 conscripts to the Swedish Army was about five times as high in the unvaccinated

as the vaccinated and that the incidence of post primary lesions was about three times.

The results of large scale tuberculin testing and B.C.G. vaccination are given in W.H.O. Reports (1950)[16] from which it is claimed that no harm has been recorded from the vaccination of over eight million persons.

A perusal of the literature leads one to conclude that the risk of developing active tuberculosis from the primary infection is reduced approximately four times by B.C.G. vaccination. There is not such good evidence that the vaccine has any protective influence against post primary infections, although some authorities are of the opinion that the lesions developing in vaccinated persons are not so severe as those in the non vaccinated. There are so many factors that control the development and progress of tuberculous lesions in man that it is difficult to assess the influence of the vaccine on post primary infection. There is, however, reason to presume that the vaccine offers considerable protection against the primary infection. Good evidence of this is found in the population on the Island of Bornholm, 49.6 per cent of whom had been B.C.G. vaccinated up to the end of 1950. As a result of increased vaccination it is claimed that tuberculosis has definitely receded, but at the same time reversion from positive tuberculin reaction to a negative reaction has increased, both in those naturally infected and the B.C.G. vaccinated. Bovine tuberculosis was eradicated from the Island in 1932. In order, therefore, to keep tuberculosis in check it will be necessary to reduce natural infection to a minimum and to maintain resistance by B.C.G. vaccination, as new cases of tuberculosis and deaths from the disease " are most frequent among the negative reactors, less frequently among the positive reactors due to natural infection and least among the B.C.G. vaccinated."[17]

Although the Bornholm evidence is of great value, we must not assume that vaccinated individuals can withstand frequent large doses of virulent bacilli. It is therefore still risky to place a vaccinated child in a heavily infected tuberculous environment. It may be able to withstand small doses of virulent tubercle bacilli, but large or even continuous small infections will eventually overcome the native and acquired resistance following vaccination and active disease will develop. It must be borne in mind that usually the only significant change that can be observed following B.C.G. vaccination is that the individual becomes tuberculin positive and nobody would agree that merely the possession of tuberculin sensitivity warrants the assumption that the individual will not contract tuberculosis.

In practice we accept the criterion that a person has been

successfully vaccinated if tuberculin sensitivity developes. This is interpreted to mean that some degree of immunity has developed. The co-relation between the degree of tuberculin sensitivity and the standard of immunity is difficult to define. It is quite certain that tuberculin sensitivity and immunity are different entities, although there is a relationship between them. It may be stated that a tuberculin positive person has a certain resistance against the infection, but a tuberculin negative reaction does not indicate an absence of resistance. In defining tuberculin sensitivity it is necessary to be clear on the strength of the tuberculin used in testing. A person of low sensitivity will be negative to high dilutions of tuberculin, but positive to low dilutions and sensitivity may be so low that it can only be detected by using B.C.G. vaccine and obtaining a mild Koch's phenomenon. All these cases can be classed as tuberculin positive but they will have vastly different degrees of tuberculin sensitivity. May we therefore ask what degree of tuberculin sensitivity must be produced by vaccination to indicate that the operation has been successful and an adequate standard of resistance has been acquired? The line is an arbitrary one and opinions vary. The World Health Organization has laid it down that all persons who do not react to 5 International Tuberculin Units (i.e. 1-2000 Old Tuberculin Mantoux test) are eligible for vaccination and if this produces a positive reaction to the same strength of tuberculin, the vaccination has been successful. The Medical Research Council require 100 T.U. for both the pre and post vaccination tuberculin tests; other authorities are content with 10 T.U. It will be seen that a good deal of confusion exists with regard to the definition of a positive tuberculin reaction. It is highly probable that the most satisfactory and practical standard to work to is 10 International Tuberculin Units.

In a young person it is usual that a low tuberculin sensitivity indicates a poor degree of resistance, but this is not true in the older age groups, particularly in cases complicated by pneumoconiosis or chronic respiratory infections. In these cases a high degree of resistance to tuberculosis can exist with a low skin sensitivity to tuberculin. Conversely the highly sensitive person to tuberculin may suffer from serious constitutional symptoms due to an allergic reaction to the infection, the severity of which will depend on the extent of dissemination of the bacilli through the body. There would therefore appear to be an optimum sensitivity that varies with age, and that in young persons it is not good to be either too hypersensitive or too hyposensitive. It is probable that a reaction of 5 to 8 mm. induration following an intradermal injection of 10 I.T.U. is the most satisfactory state of sensitivity. To maintain over a

number of years this degree of tuberculin sensitivity after B.C.G. vaccination it will be necessary for some individuals to receive periodic boosting doses of either B.C.G., or occasional small doses of virulent bacilli. If these are not received, the post vaccination sensitivity will wane and eventually disappear, although if this occurs it does not necessarily mean that resistance to tuberculous infection has also disappeared, but usually it will not be so high as in individuals in which the sensitivity has been maintained.

This generalization has its exceptions. Patients suffering from sarcoidosis are frequently tuberculin negative and their serum has the power of neutralising the ability of Old Tuberculin to produce a reaction in known positive persons.[18] As would be expected, when persons with sarcoid type of lesions develop active tuberculosis, they become sensitive to tuberculin.[19] It must be borne in mind that the tuberculin test is a measure of skin sensitivity and although antibody formation may take place centrally, the investigation is a local one and assumes that the sensitivity of all tissues is reflected in the reaction of the skin. A considerable amount of work has been done to attempt to determine to what extent the skin is the site of the sensitization process, but there are still many points on which there is disagreement.[20]

It is not surprising, therefore, that much interest has centred around the local reaction to the B.C.G. injection and it has been suggested that as about 98 per cent of those showing a local reaction at the site of vaccination are positive to 10 T.U. six weeks after, it should be possible to dispense with the post vaccination test and rely on measurement of the local B.C.G. lesion. This raises the relationship between the local B.C.G. lesion and the post vaccination tuberculin reaction.

Hertzberg (1949)[21] is of the opinion that the greater the local reaction to B.C.G. vaccination, the higher is the frequency of conversion to tuberculin positivity and also the more durable state of sensitivity.

The relationship between the tuberculin sensitivity following B.C.G. vaccination and the local B.C.G. lesion is not simple and Edwards and Palmer (1953)[22] are of the opinion that " there is only a slight tendency for large B.C.G. lesions to be followed by large tuberculin reactions and small lesions by small reactions " and that it is not possible to generalize on the matter. It does seem evident that the tuberculin sensitivity produced by a vaccine containing a high proportion of dead bacilli and a small number of living ones is higher than would be expected, and there is some evidence that dead bacilli stimulate the tuberculin sensitivity produced by the living factor of the vaccine.

From observations made by McKinstry in Jersey it appears that local reactions of under 4 mm. diameter at the site of vaccination may not be accompanied by a positive tuberculin reaction, but that those over 5 mm. in diameter are invariably tuberculin positive. Further observations are needed but it is probable that the post vaccination tuberculin test may, in the future, be dispensed with in all persons producing a local B.C.G. reaction of 5 mm. or more. The degree of sensitivity will not necessarily be highest in those that show the severest local vaccination lesions. Palmer and Meyer (1951)[23] have shown that the capacity to develop allergy after B.C.G. vaccination varies in children from different families. There is still no convincing explanation of the variation in ability to retain tuberculin sensitivity in different individuals who are not re-infected with virulent organisms. Such factors as diet, climate, race and concurrent infections may all play some part in bringing about reversion of the tuberculin reaction. In connection with this it is important to note that the haemagglutination reaction following B.C.G. vaccination shows that the antibody response is quantitatively very low and transient. It appears to bear no relation to cutaneous hypersensitivity to tuberculin.[24]

CONCLUSIONS.

The one outstanding conclusion resulting from all the work that is being done on B.C.G. vaccination and tuberculin testing is that the problem is most complex and very confusing. There is little doubt that B.C.G. vaccination is harmless and that it enhances the individual's resistance against infection by virulent tubercle bacilli. The measurement of the degree of protection is extremely difficult and can only be done in humans by estimating the incidence of disease in those vaccinated and comparing it with that found in a comparable group of unvaccinated. This is a long and tedious investigation requiring considerable organization and skilled observation. To avoid this it is assumed that the degree of skin tuberculin sensitivity produced by vaccination is a measurement of the resistance produced. How far this assumption is justified and to what extent the tuberculin reaction indicates resistance to the infection, still requires careful study.

There is general agreement that tuberculin sensitivity is a protective phenomenon and for the present it is the only test we can readily apply to provide information, but its exact significance is still unknown. There is a great field for research in this direction and it is only by careful and continued observations in all parts of the World that the very important problem of the relationship between resistance and sensitivity will be solved.

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THE STORY OF KULUVA

E. H. WILLIAMS, M.R.C.P. (Lond.)
P. H. WILLIAMS, M.R.C.P. (Lond.)

Leprosy has at some time or another affected all the races of mankind, and the feeling of pity it has usually engendered has probably been more marked than that associated with any other disease. In the West Nile District of Uganda it was therefore only a matter of time before an effort was made to care for those who had become infected. This district lies to the North West of Uganda, being bounded to the East by the White Nile and to the South and West by the Belgian Congo, and to the North by the Sudan. The Western half of the district ranges between 3,500 and 5,000 feet in height, and the Eastern half in the Nile valley averages

about 2,500 feet. Nothing had been attempted in the pre-sulphone era, so it will be seen that the development of the work presented some unusual features.

In 1946 medical missionaries of the African Inland Mission already working in the West Nile District began to contemplate leprosy work, and to search for a suitable site. This was not easy to find as the population was relatively thick, and there was some local feeling against utilising land for this purpose. Eventually, however, through the kind offices of a senior chief a site was found some seven miles from Arua, the administrative centre of the district, and named Kuluva after the local hill which is a well known landmark. Due to the feeling already mentioned 200 acres only could be obtained, and the smallness of the area delayed official recognition in some quarters for some years. Nevertheless it was the very smallness of the area leased to the Mission which led to the conception of the most unique development of the work in the end.

In 1948 the lease for the land was granted and work was started immediately, demarcating boundaries, cutting roads and erecting necessary buildings. This was made possible only through the interest of the British Mission to Lepers.

During 1949 and the first half of 1950 one residence was completed and six cottages for the accommodation of patients, but the work was slowed up by the absence on furlough of two of the staff. It was in 1949 that the concept which later came to be the most unique feature of Kuluva came into being. The leprosy problem of the West Nile was quite unknown in its extent, and no proper survey had ever been undertaken. A preliminary investigation, although later proved to be exaggerated in its conclusions, suggested the problem was considerable. Local government officers immediately began to look to Kuluva to provide a solution, but the insufficiency of land leased to the A.I.M. was a difficulty. The possibility of enlarging the lease was considered but opposed on the grounds of being contrary to accepted land policy. As a result a local officer specifically asked if we would endeavour to make suggestions to get over the difficulty. After much thought and a rapid survey of the land surrounding the Mission area at Kuluva we made the following suggestion. It was that the African Local Government of the West Nile District should take over an area of up to 1,500 acres of land surrounding our Mission site, comprising a well watered fertile valley and a fairly scattered population, and that this land should then be settled with patients on a county village basis beginning with the uninhabited portion of the area, meanwhile warning the inhabitants of the other portion that they would be expected to move away in a few years. The whole project would be

administered by the African Local Government, treatment and missionary activities being the province of the Mission. The idea had two prime advantages. Firstly it gave a means of expression to the newly awakened consciousness of the African authorities of their responsibilities towards aiding the less fortunate of their peoples, and secondly it relieved the Mission of a great weight of administrative responsibility.

In September 1950 the first patients were admitted to the Mission settlement, but they were only 30 in number and scores had to be turned away. Many of these came from nearby, and it was realised that they could be given outpatient treatment, and so this was started, and with it came another idea, giving treatment by means of the intramuscular injection of D.D.S. in watery suspension. The details of this are given later in this article. Also, because of the paucity of accommodation, it was decided to admit wherever possible lepromatous cases only, and without their families. The sulphone treatment of leprosy has completely altered the prognosis of leprosy, so that settlements need no longer be considered as asylums, but as treatment centres, with a slow but definite intake and discharge rate. Discharged patients should have a home to go to, kept going by their families during their time in the treatment centre. Essential to the working of this idea is of course the allowing of fairly frequent leave of absence.

The years 1951 and 1952 saw an extensive building programme, as yet incomplete. The accommodation in the Mission Settlement is now 102, and there is also a small general hospital, together with residences for African and European staff. Mention should be made of generous government assistance in the carrying out of this programme in addition to the aid given by the Mission to Lepers and through other voluntary contributions.

The Kuluva terrain has proved very suitable. The 200 acres Mission area is roughly lozenge shaped, divided into two parts by a hill running transversely across. The larger portion is occupied by the Mission settlement and the smaller by the hospital and residences. A considerable amount of space is taken up by the land cultivated by the patients and African staff, and the whole site is convenient of access from the adjacent African Local Government scheme which will now be described in detail.

The West Nile District has four distinct tribes in its area, totalling some 300,000 people, its local Government leading up to a District Council and its executive officers being the various grades of chief. Administrative responsibility is being gradually transferred to this body in accordance with Protectorate policy and, as mentioned before, the organisation of a settlement at Kuluva under the

aegis of the Local Government is a natural out-come of the general development of responsibility. After about two years' consideration the idea gained acceptance, and a start was made in 1951 with the penetration of the area by a road. The work was begun on the erection of a Reception Camp of 9 buildings together with houses for resident staff, and this was completed in March 1952. A safari was then undertaken through two counties in the district by the District Medical Officer and a doctor from Kuluva to select the first entrants to the settlement, 48 in all. These consisted as far as possible of lepromatous cases together with tuberculoid cases best suited for treatment. There were a number of defections and attempts at gate crashing by unsuitable cases but these difficulties were surmounted in the end. Treatment was started immediately, by once weekly injection of D.D.S., and work was also begun on the county villages for this group of patients. The village was completed in September 1952 and the patients moved in to their permanent homes, three in a house, while another safari was undertaken to select 48 more patients from another county in the district, for admission to the Reception Camp. And so the process continues to be repeated at intervals of 5 months. Each village is surrounded by an area of arable land on which the patients grow food to supplement the basic ration that they receive. The building of villages on a county basis has been found to be of great importance. There are usually more than two patients in each of different clans represented and the preservation of the clan and community spirit goes far to secure orderly functioning of each village as well as providing a safeguard against untoward incidents. The settlement is under the aegis of the African Local Government, but the actual executive responsibility has come to devolve upon the District Team which consists of various Government Officers and Africans sitting under the chairmanship of the District Commissioner. One of the missionaries at Kuluva is co-opted. Various Government departments are therefore represented and so the project also has an afforestation scheme an Agricultural scheme, and a Health scheme. This latter is concerned with the protection of springs and the proper planning and erection of villages. The work has been in operation now for over a year and has proved a very well worth while experiment with considerable promise.

Recent Government circulars have referred to the Mission settlement at Kuluva as a Primary Centre and the Local Government settlement as a Secondary Centre. A diagrammatic representation of the whole idea is appended with this article.

Some description should be given of the particular mode of

usage of D.D.S., which has been a feature of the leprosy work of Kuluva. Whereas those residing in the Mission Primary Centre have received and continue to receive D.D.S., tablets by mouth in dosage of 800 mgms weekly, others have received intramuscular injections of a watery suspension of D.D.S. The group under treatment by mouth has served as a very valuable control for assessing the efficacy of the injection technique. This is now described in detail. In the first place the reasons for the adoption of this technique should be given.

(1) Although the injection craze in Africa is a thing to be greatly deprecated and resisted by all means, yet it had been found in our experience of treating large numbers of cases of Yaws by injecting a watery Bismuth suspension, that by attention to technique a great deal of time otherwise spent in counting out and dispensing tablets could be saved.

(2) It is common knowledge that there has been and still is a widespread black market in sulphonamides in Africa, a matter that must be regarded seriously. It seemed that history might very well repeat itself in regard to D.D.S. tablets. Injection offered a way of making the illicit sale of the drug a virtual impossibility.

(3) The primitive African is liable to regard all medicines as medicine suitable for treating anything in the way of sickness. Hence if the patient is given a number of tablets to take home with him, he is quite likely to use some or all of these tablets from time to time on his sick relatives, and the dosage he should be receiving will in consequence be less than was intended.

A trial therefore was made with out-patients in the first place by injecting once weekly, 200 mgms of D.D.S. in watery suspension. In a few months we were seeing results comparable with what we were seeing with the group receiving tablets by mouth, and we felt and continue to feel that the experiment was an unqualified success and justifies our continuing the methods. Lepromatous and tuberculoid cases benefit at the same rate as similar cases receiving the drug orally.

It is perhaps interesting and instructive to trace the history of the development of this suspension. Originally a supply of D.D.S. powder was obtained and dosage begun at 50 mgms a week increasing slowly to 200 mgms a week, and the latest scheme is to give out-patients 400 mgms every two weeks. The suspension of the D.D.S. powder in water was sustained with Pulv. Tragacanth, but it tended to be lumpy and blocked needles were quite frequent. Serum No. II needles have been used throughout. The supply of powder eventually ran out so tablets were crushed and made up in the same way. The result was slightly better, but owing to the

occurrence of considerable pain at the time of injection it was decided to use normal saline instead of water. Pain diminished considerably but the lump continued. Finally the Tragacanth was dispensed with entirely and this is the type of suspension we are using now. Lumps are very unusual, the suspension is well maintained and pain at the moment of injection and during the next twenty-four hours is minimal. No abscesses over thousands of injections can be recalled. It should be particularly noted that the presence of excipient in the tablets which are crushed appears to have no effect at all, certainly no deleterious effect. A further word as to the dispensing of the suspension. The tablets are first ground to a fine powder in a pestle and mortar. Saline is slowly added and the powder worked into a smooth paste, but we have found an easier and more effective way of making the suspension than this. The powder and saline are placed together in a household article known as a ' Quikmix ' which is a cup-like vessel with a tight fitting lid. Within the cup and lid are an arrangement of ridges and whorls which are designed thoroughly to mix the contents when the whole is shaken. The effect in producing a suspension of crushed D.D.S. tablets in saline is almost magical. The resultant suspension is then sterilised by boiling for 20 minutes in a water bath. We make a fresh supply once a week. The proportion of powder to saline is 200 mgms to 1.0 cc.

The method of injection is as follows. Racks of needles are sterilised by boiling and placed in flamed trays. The patients then stand in line in groups of five or ten with the buttocks bared. A team of three then begins to operate as follows. No. 1 walks down the row cleaning an appropriate area of buttock on each patient with a suitable cleansing agent. No. 2 follows with a rack of needles. He selects a needle and plunges it sharply into each patient's buttock in turn. This method of inserting a needle is completely painless. No. 3 follows with a 5 or 10 cc syringe loaded with D.D.S. suspension. He allows a moment after the insertion of each needle before attaching the syringe and injecting in order that blood will have time to drip from the needle if the point of this has by chance hit a vein. On completing the injection he withdraws the needle and drops it into a tray. It is possible by this means to inject 100 patients in 15 minutes, which is a substantial saving of time.

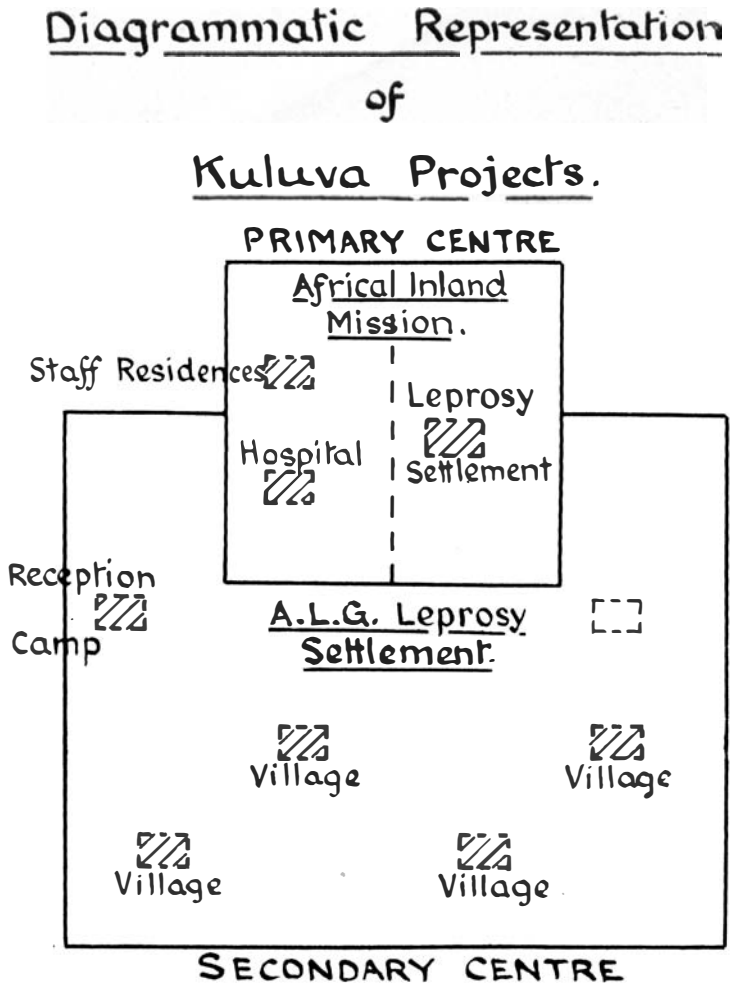
We see no reason to increase the dosage above 200 mgms per week or 400 mgms per two weeks as results seem to be sufficiently rapid. Undesirable reactions are quite uncommon, very much rarer than with 800 mgms per week by mouth, yet the results are as good. We have abandoned graded dosage and all patients (except children

who receive a half dose) receive 200 mgms per week from the beginning.

In the past two years some 900 persons have received treatment. The attendance of many however had been erratic and not a few had discontinued on their own accord. The alteration to a fortnightly regime has resulted in a more regular attendance and it is hoped that the introduction of appropriate propaganda will achieve even greater continuity.

That we have found the particular ideas and methods set out in this article effective does not mean to say that they would universally be so. Our experience is limited to the West Nile District of Uganda only, but as a story of a work with some unusual features it may be of interest to other leprosy workers.

Our thanks are due to the Honourable Director of Medical Services, Uganda for permission to publish this article.



AN EVALUATION OF NEW TREATMENTS AND OTHER FACTORS IN LEPROSY

Dr. W. S. Davidson,

To estimate the value of treatment in leprosy when that treatment is applied for a matter of months and not years is like estimating the rate of change of water in a tidal estuary. The whole picture is confused by the repeated ebb and flow, the constant remission and recrudescence characteristic of the disease.

An estimate based on the number of cases improved versus the number of cases not improved is fallacious to the extent that it merely indicates the different condition of the patients at two points of time without in any way measuring the true progress of the disease under the treatment or indicating how far any progress is likely to be maintained. It is common practice to find in a periodic review of one's patients that in whatever way we evaluate their progress most cases will show from time to time a worse picture than in the previous review.

If, therefore, we are to estimate the value of a treatment applied over a short period of time we can so influence the result as to make its significance worthless by disregarding the natural periodicity of the disease in selecting a time for survey, albeit unintentionally, when an unusual proportion of our patients are in remission or recrudescence.

Early estimates of the value of new treatments must however be made and the value of our first observations then allowed to await the proof of time.

In this paper an attempt has been made to evaluate five different treatments carried out for one year, and other factors of importance in leprosy. To minimise the influence of periodicity the individual has been disregarded and an estimate of the general progress of the disease in the group or series has been aimed at. Progress has been reduced to a numerical index and relapse or negative progress in an individual is a deduction from the positive score of progress in his group or series.

The analysis is concerned only with the various categories of lepromatous leprosy; where individuals with both lepromatous and neural lesions are involved, progress, positive and negative, does not in any way refer to the latter.

The clinical picture and the smear count were the criteria indicative of progress. Marks one to three were awarded for each,

thus: slight or moderate improvement—one mark; marked improvement—two marks; all lesions completely gone—three marks. The smears were taken from nose, ear lobes, supraorbitals and other skin lesions and the patient marked +, + +, + + + according to the highest smear count obtained. It was therefore necessary for a patient showing + + + in smears from various sites to show improvement at all sites before being classified as + +, and thereby gaining a mark. A change from + + + to + +, and + + to +, gained one mark; and + + + to +, and + to —ve, gained two marks; + + + to —ve and + + to —ve gained three marks.

The marking was reversible in that deterioration in clinical picture or smear counts obtained corresponding minus marks.

A similar system was employed for R.B.C. counts and Haemoglobin estimation.

Marks 1 to 3 were also given for severity of toxic manifestations and lepra reactions. There were of course no minus markings in these categories.

Marks then, for the clinical picture and smear count indicated progress under treatment. In these two items the total possible for any one individual to gain was six. In actual practice the highest score was five marks. Plus and minus were totalled for the group and that total divided by the number in the group, thus giving the index of progress in the group or the average gain per individual.

The treatments under review are:—

1. Sulphetrone intramuscularly 4 c.c. of a 50% solution, twice weekly. The full dose normally reached in four weeks from commencing treatment.
2. Sulphetrone by mouth 3 g. daily. Full dose reached in three months.
3. D.A.D.P.S. 200 mg. daily. Full dose reached in two months.
4. Neustab (Thiacetazone) A Series.
   1st month 25 mg. daily.
   2nd-7th month 50 mg. daily.
   8th-12th month increasing to 200 mg. daily reached during 12th month.
5. Neustab (Thiacetazone) B Series.
   Commenced with 25 mg. daily and reaching full dose of 200 mg. daily in three months.

In treatments 2, 3 and 5, one day's rest given every week and one week's rest after every two months.

An indication of the efficacy of these treatments is given in col. 6 of Table I. Intramuscular Sulphetrone and D.A.D.P.S. are

almost equally effective with indices of 2.16 and 2.18 respectively. Col. 2 of Table II, however, indicates that the D.A.D.P.S. is more toxic than the intramuscular sulphetrone with an index of .24 compared with the latter's .14.

The Oral Sulphetrone showed a comparatively poor result with an index of only 1.65. This does not necessarily indicate that the drug is relatively ineffectve. It may be that the dose of 3 g. daily is not adequate. Table II supports this interpretation as it shows no evidence of toxicity from this treatment, whereas there were varying degrees of toxicity in all other treatments.

Neustab Series A was an early use of this drug and the dosage is evidence of exaggerated caution. The result, a .35 index, shows clearly the need for adequate dosage when compared with Series B. So disappointing were the results in Series A that treatment in that series was switched to sulphetrone at the end of 13 months' treatment. The majority then showed rapid improvement.

Neustab B Series is unfortunately rather small and can only be taken as an indication of what might be expected from adequate dosage of this drug. The resulting index of 2.87 is by far the highest of the treatments reviewed. As regards adequate dosage it is of interest to record that the indices for Neustab Series B and the D.A.D.P.S. Series at the end of six months' treatment were respectively .87 and .91. The Neustab did not overtake and pass the performance of the D.A.D.P.S. until the second six months of treatment. This may partly be due to full dosage of D.A.D.P.S. being reached 4 weeks before that of Neustab.

Neustab both in the low and the high dosage series gives higher toxicity than any of the other drugs, Neustab B Series giving an index more than 2½ times that of intramuscular sulphetrone.

It will be seen from Table II that there is no correlation between toxicity and effect on R.B.C.s or haemoglobin. Indications of toxicity were, in the main, dermatitis and signs of hepatic damage.

Other factors investigated which may be thought to influence the result of treatment are shown in Table I. Cols. 1 and 2 are two different groupings of the cases according to lesions or type of leprosy.

In Col. 1 they have been divided into L or lepromatous group with no neural lesions, and LN, a group with both neural and lepromatous lesions.

In Col. 2 LL indicates the diffuse spreading non-resistant type of leprosy and diffuse nodular leprosy; T represents the tuberculoid or more resistant types with circumscribed lesions. The differentiation was made purely on the macroscopic appearance.

The bottom line of the table summarises the position for all

groups of treatment in the comparison of the various factors investigated. It will be seen that there is little significant difference in the results of treatment between the lepromatous and the mixed types but the tuberculoid improved more than the diffuse lepromatous type. The difference however is not statistically significant.

In Col. 3 the cases are divided into those that gave a +ve lepromin reaction at the beginning of treatment or developed it during treatment and those that gave —ve reactions or became —ve during treatment. Here the index for lepromin +ve of 2.05 and lepromin —ve of 1.74 gives some support to the theory that a +ve reaction is an indication of resistance. But again, the difference between the indices when tested statistically is not significant.

There is also in Col. 4 little difference between those showing lepra reactions and those that do not. This does not necessarily mean that an individual who has a lepra reaction may not eventually show an improvement from it. It merely means that in the group that has reactions there is no difference in the overall improvement to that in the group that does not have lepra reactions.

In Col. 5 cases have been divided into two groups depending on whether their haemoglobin was above 13 grammes or was 13 grammes or below per 100 ml. The standard was that shown at commencement of treatment or attained soon afterwards and maintained throughout the treatment.

The index of improvement in the high Hb. is 83% better than that in the low.

Some idea of the significance of these indices may be obtained as follows. They are derived from our computation that 80 cases of high Hb. obtained 174 progress marks and 41 cases of low Hb. cases obtained 49 marks. The maximum number of marks obtained by any patient was 5 and that number was a possibility for all patients; therefore, the 80 cases had a possible of 400 and 41 cases a possible of 205. The significance of our figures then lies in the testing of the proportions: 174/400 and 49/205. The difference between these proportions is five times its standard error. In other words, the difference between the progress indices for high and low haemoglobin cases is highly significant.

Tested in a similar manner the differences between the lepromin indices and between the indices of LL and T types are only equal to their standard errors and cannot therefore be considered significant.

Another point which is not without significance with regard to the good result shown by Neustab in the B Series emerges from a study of Table I. All the 8 cases in that series were of the more resistant to treatment LL type, but 7 of the 8 were in the high Hb.

group and the high marks for the series were obtained entirely from these 7, the remaining member of the series was low in Hb. and contributed no marks.

It is extremely difficult to arrive at the real implication of this significant difference in the response to treatment in low and high haemoglobin cases. But some attempt must be made to ascertain its real meaning so that we can apply that knowledge to a proper interpretation of the varying results from treatment.

The haemoglobin may be reduced by extrinsic or intrinsic factors.

Factors extrinsic to the disease are malnutrition and chronic disease other than leprosy. Intrinsic factors are the leprosy itself and the toxic effect of the drugs used in treatment.

All the cases reported on had treatment with iron and vitamins prior to specific treatment. Anti-anaemia treatment was maintained throughout the course. There is no malaria among the population and, apart from yaws, little or no chronic disease.

Extrinsic factors were therefore negligible. If the anaemia arose from the leprosy itself it may indicate that there is a type of leprosy that produces anaemia and is also resistant to treatment. Our other classifications of the disease including clinical picture, lepromin reaction and lepra reaction have, however, shown no other characteristic giving a division similar to that of anaemia. It is therefore somewhat unlikely that we are dealing with a special type of leprosy. In treatment also it is difficult to see why the lower dose of Neustab in A Series should cause anaemia rather than the bigger dose in B Series. Similarly, the Oral Sulphetrone is associated with a greater decrease of haemoglobin than the more toxic doses of Intramuscular Sulphetrone and the D.A.D.P.S. (Table II).

We are then faced with the alternative that the poor results in Sulphetrone Oral and Neustab A Series were due to a chance distribution of an unusually large number of low haemoglobin cases in these series or that the dosage of the drugs in these series was such as to produce low haemoglobin. The second alternative seems the more probable and gets some confirmation from Table III.

In Table III 12 cases were treated for 2 years with Oral Sulphetrone 3 g. daily. The index for haemoglobin decrease is again high and the greater proportion again fall in the low haemoglobin group. The index of the 7 cases in the low haemoglobin group treated for two years is lower than the index for the 7 cases in the high haemoglobin group treated for one year on the same treatment.

The over-all impression obtained is therefore that where leprosy is treated with a toxic drug in doses that are sub-optimal there exists

a summation of the toxic effect of both the disease and the drug causing a decrease in the haemoglobin which is detrimental to the beneficial effect of the treatment.

As the geographical distribution of leprosy coincides with that of secondary anaemia from malnutrition, malaria and other chronic diseases, it may not be irrelevant to suggest that the importance of haemoglobin in treatment may also apply in prevention. Increased haemoglobin levels in populations at risk may lead to a reduced incidence of leprosy.

SUMMARY AND CONCLUSIONS :

121 cases of leprosy were divided into five series and given different treatments for one year.

A further series of 12 cases had treatment for two years.

The results are analysed numerically and would appear to indicate the following conclusions:—

1. A short series on Neustab 200 mg. daily gave the best result.
2. Intramuscular Sulphetrone and D.A.D.P.S. in much larger series gave equal results, not quite so good as the Neustab.
3. Intramuscular Sulphetrone was the least toxic and Neustab the most toxic.
4. Sulphetrone by the oral route 3 g. daily gave comparatively poor results due largely to a fall in the haemoglobin of the patients.
5. Neustab in doses (as stated) less than 200 mg. daily was ineffective and also was associated with low haemoglobin.
6. Haemoglobin above 13 g. is necessary to obtain the best result from treatment.
7. Under dosage or sub-optimal dosage is associated with a fall in haemoglobin far more than occurs with full dosage.
8. It is suggested that low haemoglobin may predispose to the development of the disease in populations at risk.
9. With regard to improvement of the disease under treatment, no significant advantage was shown between the various types of leprosy or between lepromin + ve and lepromin —ve cases or between those with lepra reactions and those without.

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Published with the permission of Dr. L. Henzell, Commissioner of Public Health, W.A. The patients are inmates of Derby Leprosarium, W.A., and to Dr. Grigoroff, Mother Alphonsus and Sister Angela of that institution must go to entire credit for carrying out the treatment and examinations and compiling the reports that have been the basis of this analysis.

TABLE I.
(One year treatment)

		1. L.	1. LN.	2. T.	2. LL.	3. Lepromin Reac. +ve	3. Lepromin Reac. —ve	4. Lepra Reaction +	4. Lepra Reaction Nil	5. Haemoglobin High	5. Haemoglobin Low	6. TOTALS
Sulphetrone Intramuscular ...	No. Cases	21	22	5	38	14	29	3	40	30	13	43
	Marks	52	41	11	82	24	69	4	89	72	21	93
	Index	2.48	1.86	2.2	2.16	1.71	2.38	1.33	2.22	2.4	1.62	2.16
Sulphetrone Oral	No. Cases	7	10	4	13	7	10	6	11	7	10	17
	Marks	8	20	7	21	13	15	6	22	18	10	28
	Index	1.14	2	1.75	1.61	1.86	1.5	1.0	2.0	2.57	1	1.65
D.A.D.P.S.	No. Cases	18	15	8	25	10	23	12	21	24	9	33
	Marks	34	38	25	47	30	42	27	45	50	22	72
	Index	1.89	2.53	3.12	1.88	3.0	1.83	2.25	2.14	2.08	2.44	2.18
Neustab A Series	No. Cases	4	16	7	13	7	13	2	18	12	8	20
	Marks	1	6	6	1	4	3	2	5	11	—4	7
	Index	.25	.38	.86	.07	.57	.23	1	.28	.92	—0.5	.35
Neustab B Series	No. Cases	3	5	—	8	3	5	3	5	7	1	8
	Marks	7	16	—	23	13	10	10	13	23	0	23
	Index	2.33	3.2	—	2.87	4.33	2	3.33	2.6	3.29	0	2.87
Neustab A & B Series combined	No. Cases	7	22	7	21							29
	Marks	8	22	6	24							30
	Index	1.14	1.0	.86	1.14							1.04
All Treatments	No. Cases	53	68	24	97	41	80	26	95	80	41	121
	Marks	102	121	49	174	84	139	49	174	174	49	223
	Index	1.92	1.78	2.04	1.79	2.05	1.74	1.88	1.83	2.18	1.19	1.84

LL. : Lepromatous and nodular leprosy.
T. : Tuberculoid leprosy.

TABLE II

(One year treatment)

	1. Number of Cases	2. Toxicity		3. Lepra Reactions		4. Decrease in HG.		5. Decrease in RBC	
		Points	Index	Points	Index	Points	Index	Points	Index
Sulphetrone Intramuscular	43	6	.14	7	.16	14	.33	19	.44
Sulphetrone Oral ...	17	0	0	10	.59	26	1.53	16	.94
D.A.D.P.S.	33	8	.24	15	.45	15	.46	20	.61
Neustab A Series ...	20	6	.3	4	.2	15	.75	13	.65
Neustab B Series ...	8	3	.37	4	.5	0	0	4	5
Total all treatments ...	121	23	.19	40	.33	70	.58	72	.59

TABLE III

TWO YEAR'S TREATMENT WITH ORAL SULPHETRONE.

	High Hb.	Low Hb.	Total	Haemoglobin Decrease
No. of Cases	5	7	12	12
Marks	15	16	31	9
Index	3.0	2.28	2.58	.75

LEPROMATOUS NEURITIC LESIONS, THEIR GREAT INCIDENCE IN CERTAIN SENSORY AND MOTOR BRANCHES, AND THE TREATMENT

DR. MARIO GUADAGNINI.

LEPROMATOUS NEURITIC LESIONS

We wish to refer to the hypertrophic lepromatous neuritic lesions and their pain symptomatology, which is a clinical aspect bound up with anatomical factors. We propose to describe the surgical form of attack on the neural and paraneural picture.

The cases which we present were taken in the acute or subacute period, when the nerve feels enlarged, painful, tense, and of increased consistency, with the surface apparently regular and even, or deformed by the presence of circumscribed nodules which occupy the inner nerve. The tendency which certain sensory-motor nerve branches have to localize the processes of reactional hypertrophic neuritis in particular parts of their course, we interpret as being related to the existence of anatomical paraneural factors which affect the nerve in areas contiguous to the articulations: there the muscle masses disappear, being substituted by ligamentous insertions; there the proximity of osseous planes and aponeuroses do not permit of a uniform distension of the nerve in the first stages of the diffuse neuritis, so that the motor branches, in spite of undergoing the same blood invasion during the reactional bacillaemias, do not give any appreciable painful symptomatology. This condition one supposes is due to their not having suffered compression in their course.

The sensory-motor nerves which become tender and hypertrophic are, in order of frequency, the *cubital*, which suffers compression in its passage through the inner region of the elbow as it enters the epitrochlear-olecranon tunnel: then the *external popliteal* when it turns over the head of the fibula where it is imprisoned by the aponeurosis; then the *median nerve* which is exposed to the same conditions in the zone of wrist flexion as it crosses the anterior annular ligament of the wrist: finally the *posterior tibial nerve* in its passage through the tunnel formed by the internal tarsal ligament in the internal retro--malleolar region. It is always above the compressed portions of the nerve where occurs the enlargement of the nerve, with a dilatation of the epineural capillaries inducing a varicose aspect, accompanied by a stagnation of blood circulation in the neural vessels which adds to the active local congestion. This

situation contrasts on the other hand with that of the compressed part of the nerve, which remains free of congestion and thickening. For this reason we do not limit our intervention to freeing the nerve, but seek to eliminate or relieve also the paraneural factors which cause the compression.

SURGICAL CONSIDERATIONS

Surgical intervention comprises the isolation of the nerve, its decapsulation and neurolysis, with elimination of the factors causing neural compression.

The nerve is approached by an incision which embraces the thickened tender part together with the compressed sector. Having incised the superficial planes and isolated the nerve, two sutures are passed below the nerve and brought to the extremities with the object of holding the nerve firm in the procedure of neurolysis.

The paraneural aponeurotic tissues are incised in the whole area of compression of the nerve so as to attain its liberation, so that for the *cubital* one opens the epitrochlear tissue and its aponeurotic prolongation of the anterior cubital muscle; for the *external popliteal* one opens the tibio-peroneal aponeurosis; for the *median nerve*, the anterior annular carpal ligament; for the *posterior tibial*, the internal tarsal ligament.

Having decompressed the nerve, one begins the neurolysis with the decapsulation by means of a longitudinal incision of the epineurium or sheath, including the endoneurium which is divided almost in two halves, all this being carried out with the nerve held tense by means of the two sutures placed at the ends. The epineurium is dissected and separated from the underlying plane of the endoneurium, on which are carried out other longitudinal incisions which are adjusted to the degree of thickening of the nerve. Having completed the neurolysis, we are accustomed to reconstruct the epineurium in the whole of its decapsulated course with interrupted stitches. Finally, as suggested by Dr. Robert G. Cochrane during his visit to the Sanatorium Sommer, in two cases we have carried out total resection of the epineurium, with good results.

We think it of interest to detail some particulars of technique relating to the various sensory-motor branches concerned, beginning with the *cubital nerve*, which provides the highest percentage of hypertrophic neuritis. In order to attack this nerve we place the patient on the operating table in the supine position, with his arm extended and rotated forward so as to expose the epitrochlear-olecranon region. The incision extends from the middle third or lower third of the inner surface of the arm towards the hypertrophied portion of the nerve, and is carried on as far as the forearm in a

curved line above the course of the epitrochlear-olecranon furrow. The skin having been incised and the superficial fascia exposed, one makes an opening immediately above the epitrochlear tendon or entrance to the tunnel in order to expose the nerve to view, and where is introduced the half-opened scissors in order to push it upwards and open up the internal intramuscular partition wall of the arm, a space which the cubital nerve traverses. With a similar manœuvre in the opposite way towards the forearm one opens the epitrochlear corridor in its whole length as far as the fibres of the anterior cubital muscle. With this technique one simplifies and facilitates the isolation of the nerve in all its affected course, including the compressed portion, without damaging it by laborious dissections, especially when the reactionary perineural processes generate organized adhesions to the surrounding tissue planes, as happens in the case of the cubital nerve in the middle or lower third of the arm.

Having opened the epitrochlear-olecranon tunnel (the cause of the nerve compression because of its anatomical characteristics of being in the form of an inextensible osteo-fibrous tube and having a scanty lining of adipose tissue), the nerve is freed and loosened from the narrow bed formed by the tunnel: then the nerve is displaced and transposed in front of the internal condyle or epitrochlea. For that purpose, previously, the cutaneous plane which covers the internal surface of the elbow in relation to the epitrochlea is freed from the underlying superficial muscular fascia, so as to make a place for the new bed which the cubital nerve should now have in exchange for its pre-epitrochlear course.

The transposed cubital nerve is fixed in front of the epitrochlea, making use of the cellular fascia, which we dissect from the internal attachments of the elbow. In its new course the nerve shortens its curve, its stretchings in the movements of arm flexion are diminished, and the compressions due to the tunnel are eliminated.

Concerning the *external popliteal nerve*, which is frequently involved, it can be felt thickened within the biceps-crural muscle in the region of the popliteal fossa. Here the phenomena of compression occur when the nerve turns through half a circle about the head of the fibula, a place where the tibio-peroneal aponeurosis flattens it against the bony surface, so that the nerve takes a tape-like form. In the operation, the tibial aponeurosis is incised up to the bifurcation of the nerve into its two branches, the anterior tibial and the musculo-cutaneous, among the fibres of the long lateral peroneal muscle, respecting as far as possible the branch of the cutaneous peroneal which starts further up. At the end of the operation the neurolysis is completed with the partial resection of the

edges of the tibial aponeurosis, which are left without being sutured.

The *median nerve* localizes the processes of neuritis in the flexor aspect of the wrist, and the circumscribed and fusiform hypertrophy of the nerve can be felt among the major and minor palmar tendons and sometimes be made to stand out when the wrist is placed in hyperextension. The compression phenomena are produced when the nerve passes through the medio-carpal canal, along with the flexor tendons of the hand; this canal is formed by the anterior annular ligament of the wrist, which surrounds the nerve and the tendons in a fibrous semi-circle. In the operation the said ligament, which is tough and firm, is incised in its whole breadth and the incision goes from the lower part of the wrist to the base of the palm, where again the nerve has a degree of freedom.

Finally the *posterior tibial nerve,* sometimes forgotten in clinical examination, is felt tender and increased in volume between the internal malleolus and the tendo Achilles; in its course through the tissues of the instep it is accompanied by the tibial vessels until it reaches the internal tarsal ligament. This ligament is formed by the fusion of the superficial and deep aponeurosis of the region, which establish four fibrous tunnels, in one of which the nerve is imprisoned by the deep planes formed by the calcaneus bone, and it is in this course that it is first subject to compression in the neuritic reactions. In the freeing of the nerve the tarsal ligament is opened in the whole course of the tunnel, in its characteristic curved course.

CONCLUSION AND STATISTICS

In the Sanatorium Sommer de Rodriguez, Argentina, there have been carried out 198 surgical operations for neuritis, based on the different clinical forms and evolutionary stages of all the cases subjected to operation, 146 correspond to the acute or subacute reactional lepromatous type with painful hypertrophy, of variable intensity, and preceded by cutaneous activity in the form of erythema nodosum or polymorphic erythema, the clinical type with which we have been concerned in this paper. The distribution of the operations for neurolysis and decompression on the various sensory-motor nerves is as follows:—

Cubital nerve, 103.
External popliteal, 24.
Median, 15.
Posterior tibial, 4.

The patients subjected to operation had been suffering from neuritis of painful nature from a few days to a year or more. Some had had partial remissions followed by sharp new exacerbations, of which opportunity was taken to intervene.

The pain-removing effect of the decompression and neurolysis was immediate in all the cases above the hypertrophied part of the nerve. The distal disturbances, such as areas of painful hyperaesthesia, parasthaesia, and cutaneous blunting of sensation, showed less apparent favourable modifications, but were appreciable mostly in the post-operative period, with diminution or disappearance of the pains in 50 to 55%.

In this account we have not made note of trophic modifications consequent on freeing the nerve.

In the total of those operated on we have had 24 relapses of pain, in patients between the first and third year and in whom it was necessary to reintervene, also patients with marked cutaneous activity. The nature of the relapses was that there symptoms were milder with less pain and the inflammatory reaction was more circumscribed in the affected area.

The distribution of the relapses was:—

Cubital, 17.
External popliteal, 5.
Median, 2.
Posterior tibial, 0.

A second operation re-established calm, except for 2 cases of neuritis of the cubital which required a third operation.

SUMMARY. There are certain sensory-motor nerves which are greatly predisposed to the processes of painful hypertrophic neuritis.

We interpret the pathology as bound up with certain anatomical perineural relations constituted by aponeurosis, ligaments, and osseous planes which act as compression factors on the nerve in the initial processes of the diffuse neuritis.

These painful forms of neuritis are suitable for surgical intervention, which is a treatment directed to the relief of pain and the amelioration of the trophic lesions. To this end are carried out decapsulation and neurolysis, with elimination of the perineural anatomical factors in compression.

The pain-removing action in the operated portion of the nerve is immediate in all patients: this is less marked in distal disturbances. With regard to the distal manifestations corresponding to the nerve branch affected, the improvement varies with the timeliness of the operation and the valuable effects of post-operative care.

NOTE.—The photographs have been made by the Rev. Chaplain of the Sanatorium Sommer, Señor Joaquín Prochaka, to whom my thanks are due.

(Translation from the original Spanish.—J.R.I.)

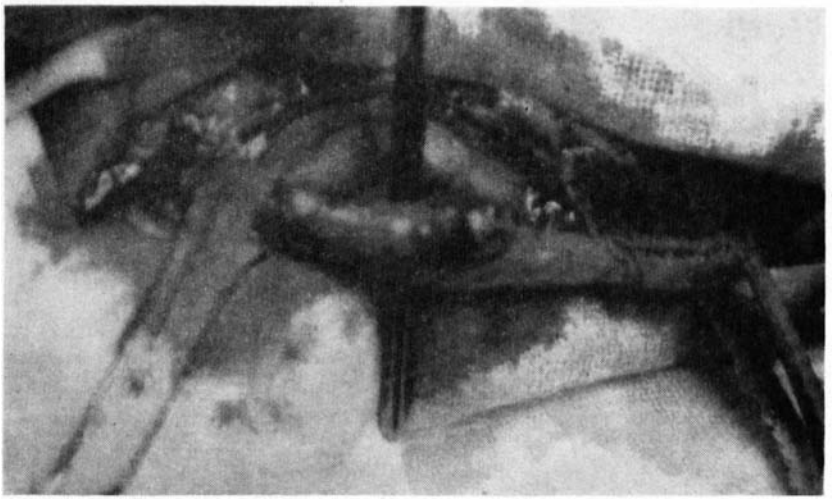

FIGURE N.1—Ulnar nerve in reaction, with two nodules projecting and multiple vessels with a varicose appearance.

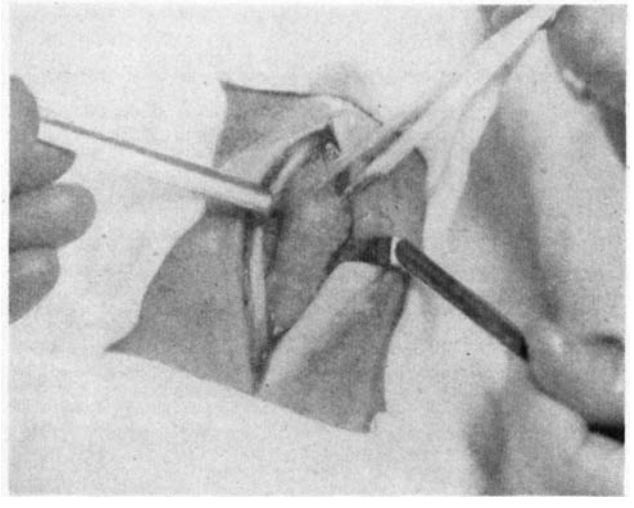

FIGURE N.2—Hypertrophied median nerve above the annular ligament on the anterior aspect.

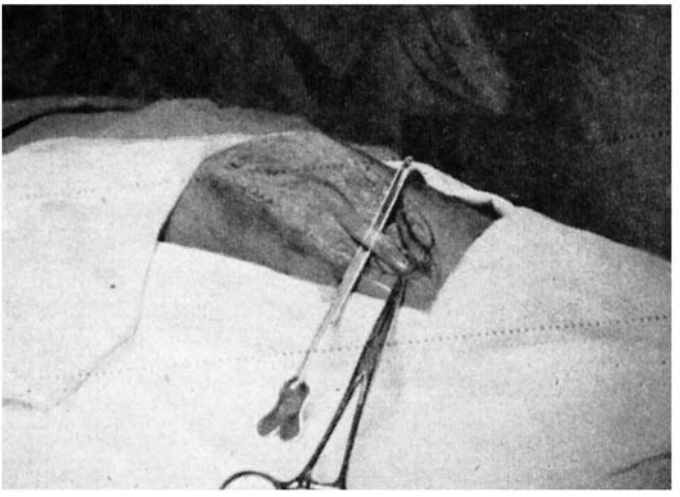

FIGURE N.3—Hypertrophied ulnar nerve on the epitrochlear condyle.

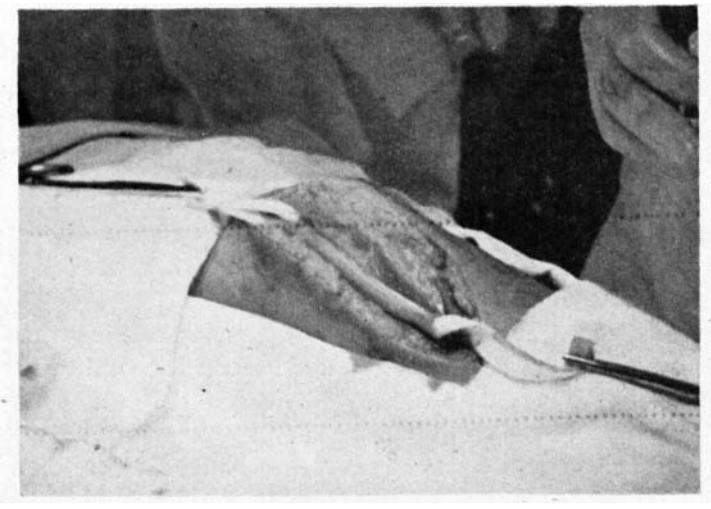

FIGURE N.4—Hypertrophied ulnar nerve displayed from its bed.

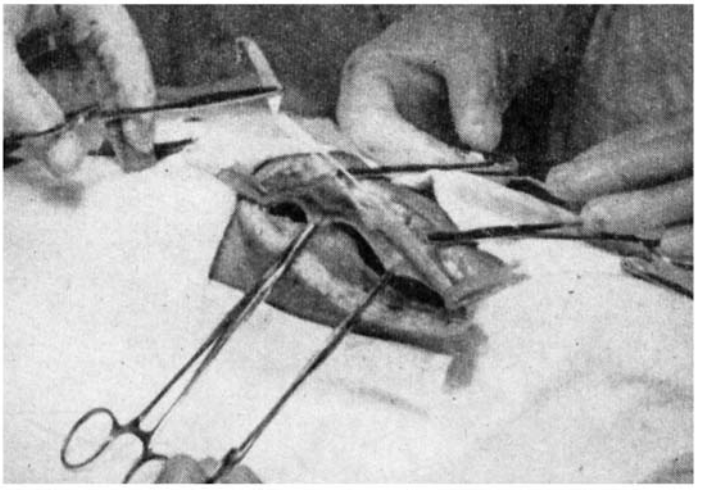

FIGURE N.5—Ulnar nerve with the epineurium opened.

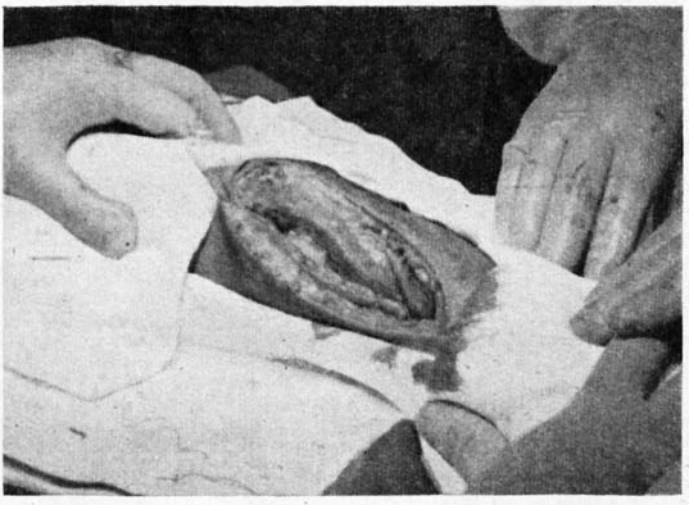

FIGURE N.6—Ulnar nerve with its epineurium reconstructed.

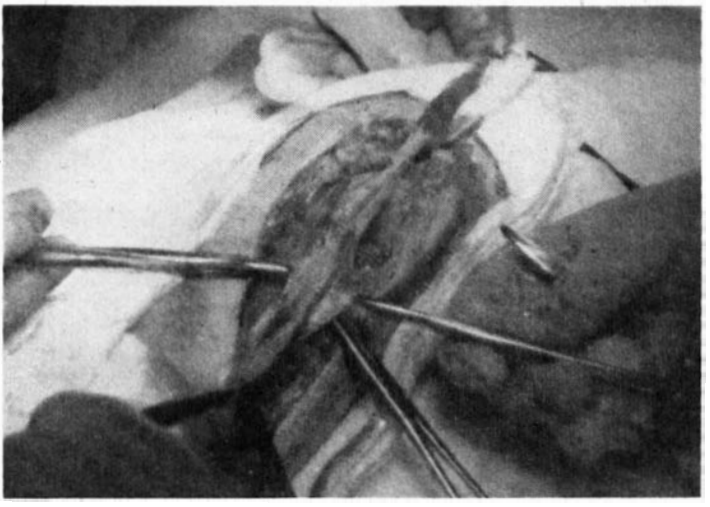

FIGURE N.8—External popliteal nerve with the capsule removed. Notice the flattening of the part which passes round the head of the fibula.

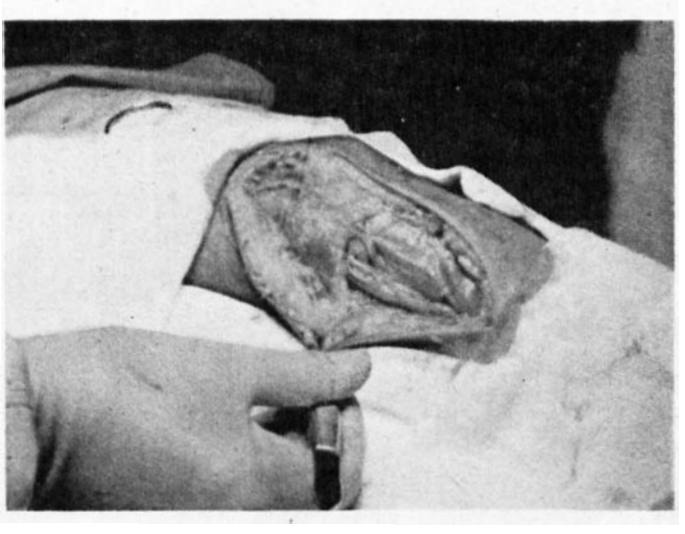

FIGURE N.7—Ulnar nerve displaced, and fixed by a portion of cellular fascia.

TREATMENT OF LEPROSY WITH 'SULFON-CILAG'

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In this short paper the results of 19 months therapy of cases of lepromatous leprosy with 'Sulfon-Cilag,' administered parenterally is presented.

The Drug: Sulfon-Cilag is a derivative of the parent substance, diamino diphenyl sulphone (DDS) with the structural formula,

$$H_2N \langle\!\rangle SO_2 \langle\!\rangle NH{-}CH_2{-}COONa$$

The sulphone $-N-$acetate molecule contains 75.6% of DDS. This substance is water soluble and the Ph of the injectible solution of Sulfon-Cilag is 7.3 to 7.7.

The special advantage of this new sulphone derivative appears to be the utilisation of the bactericidal properties of the active substance under favourable conditions of toxicity. The glucose-bisulphite complex for bacteriological agents is considered unsuitable since relatively energy-rich substances like sugar, alcohol, etc., by promoting oxidative processes in bacterial cells may oppose the inhibitory action of the chemotherapeutic agent on the proliferative apparatus of the bacteria. On the other hand, with Sulfon-Cilag, it is claimed, that by virtue of the low energy grade of its carrier substance, its ability to release the reductive processes and thereby have an inhibitory action on bacterial proliferation will be more pronounced.

THE MATERIAL

Fourteen cases, all adults, of lepromatous leprosy of varying severity were chosen for the investigation. All these cases, except one, had been treated previously either with hydnocarpus remedies, or one or other of the sulphone group of drugs.

THE METHOD

The 14 patients chosen for this investigation were divided into three groups, A, B, and C. Group A, consisting of 6 patients, was treated with daily injections of Sulfon-Cilag, 5cc intravenously leaving out Sundays. Group B, comprising 4 patients, was given 10cc of Sulfon-Cilag subcutaneously twice a week. Group C, with 4 patients, was treated with 5cc of Sulfon-Cilag subcutaneously every day for 6 days in the week.

THE DOSAGE

Sulfon-Cilag was supplied in ampoules of 5cc containing 0.5G of the active substance. Even though the manufacturers of this drug suggested a daily dose of 1G intravenously, slowly increasing it to 2.5G daily, it was considered advisable to plan out the investigation with groups of patients who received the drug by two different routes and in three different dosages. Taking into consideration the very high DDS content of this drug (75.6%), a dose of 0.5G Sulfon-Cilag intravenously or subcutaneously every day was considered suitable and safe. In addition a third group was added wherein the patients were given 10cc of Sulfon-Cilag (1G) subcutaneously twice a wek. The drug was administered continuously without rest periods so long as supplies were available.

THE RESULTS

Clinical trials with the drug were commenced in March 1949 and patients were treated for periods varying from 1.0 to 18.5 months. The treatment has to be discontinued for two months for groups A and C owing to lack of supply of the drug. It should be mentioned here that in spite of the break of two months in treatment, there was no deterioration in the patients' clinical condition during that period nor was there any untoward effect when treatment was recommenced.

(a) *Clinical*

It was the general impression that the drug produced perceptible clinical improvement in most of the cases. There was subsidence of infiltration in the lesions, and nodules showed considerable shrinking, leaving behind loose, redundant skin. It was such favourable results which kept the patients so regular in attendance.

(b) *Bacteriological*

It was obvious that the improvement in the bacteriological status of the patient was not commensurate with the clinical improvement. Secondly, while four cases were ' much improved ' bacteriologically, only one became ' negative.'

INCIDENCE OF COMPLICATIONS

The general impression about Sulfon-Cilag was that it was very well tolerated by most of the patients. Out of the 14 cases treated for periods varying from 1.0 month to 18.5 months, (a) severe and intractable neuritis was seen in one patient (A3); (b) severe lepra reaction in two cases (A4 and B3); and (c) anaemia of moderate severity developed in one case (C4). In case (A3), the neuritis affecting the right ulnar was so very severe that the patient stopped away from treatment.

CASE HISTORIES.

GROUP A—5cc Sulfon-Cilag intravenously every day for 6 days in the week.

Patient A1. Hindu, male, 29 years. A case of moderate leproma of 9 years' duration. Had previous treatment with Hydnocarpus remedies, indigenous drugs, Promin, Soluthoizole and Diasone.

Commenced treatment with Sulfon-Cilag on 14-3-1949 with a bacteriological index of 1.06. Continued treatment regularly except for a break of two months when supplies of the drug ran out. Total dosage of the drug administered: 215.0G. Did not show any untoward sign during the treatment. At the end of the therapy, patient appeared ' much improved ' clinically, though the bacteriological index registered an increase (1.56).

Patient A2. Muslim, male, 24 years. A case of moderate leproma with a few nodules here and there, the duration of the disease being 11 years. Patient was treated with hydnocarpus remedies. Got better. Relapsed later; took to Unani treatment and got steadily worse.

Commenced treatment with Sulfon-Cilag on 15-3-1949 with a bacteriological index of 2.25. Continued treatment regularly without any untoward sign but had to stop treatment in November 1949 due to development of ' infective jaundice.' Restarted treatment in February 1950 and continued till the drug ran out of stock in November 1950. Total amount of the drug given: 217.0G. The patient had an uneventful course of treatment. The nodules shrank in size; the infiltration cleared up leaving behind areas of mottled hypo-pigmentation. The bacteriological index came down to 1.25.

Patient A3. Hindu, male, 21 years. A case of macular leproma of 6 years' duration. Had routine hydnocarpus treatment haphazardly for six years.

Commenced treatment with Sulfon-Cilag on 10-3-1949 with a bacteriological index of 0.12. On 9-6-1949, patient complained of fever in the evenings, indicative of possible onset of lepra reaction. Symptomatic treatment was given and the drug was continued. On 20-6-1949, patient complained of severe pain on the course of the right ulnar. On palpation the nerve was found swollen and tender. The patient was started on a course of antimony injections (potassium antimony tartrate) 00.2G intravenously on alternate days for 3 injections and 00.4G intravenously for the next three injections. On 22-6-1949, the neuritis became very severe and hence Sulfon-Cilag was withheld. The patient completed a course of potassium antimony tartrate without any relief from the neuritis. Thereafter, the patient did not attend the Clinic and on 14-9-1949, he was reported to be suffering from ' fever ' for a week. On

17-10-1949 the patient was coaxed into restarting the treatment on a smaller dose of the drug; but after the injection on that day, he disappeared. Total quantity of the drug administered: 41.5G.

Patient A4. Hindu, male, 18 years. A case of advanced nodular leproma of 12 years' duration. Had irregular hydnocarpus treatment on and off.

Commenced treatment with Sulfon-Cilag on 18-4-1949 with a bacteriological index of 2.68. Continued treatment till 17th December 1949, when he was given rest due to lack of supply of the drug. On 9-1-1950, 22 days after the treatment was temporarily stopped, he reported with severe lepra reaction. On that day he was given another injection of Sulfon-Cilag to augment the reaction and then put on dihydrostreptomycin, 1G intramuscularly once a day, in order to study, incidentally, the effect of this anti-biotic on lepra reaction and the disease. On 20-1-50, the temperature touched normal but streptomycin was continued till 21-2-50; in all 40G of streptomycin being given. The bacteriological index at commencement of streptomycin treatment was 1.65 and at the end of the therapy, it was 1.44. Treatment with Sulfon-Cilag was recommenced on 21-3-50 and continued regularly till 22-7-50 and then discontinued since the patient went out of town. Total dosage of Sulfon-Cilag administered: 139.5G. At the time the treatment was discontinued (July '50) the patient appeared ' much improved ' clinically, even though bacteriologically he was only slightly improved. (B.I. 2.00.)

Patient A5. Hindu, female, 25 years. A case of moderate leproma of 12 years' duration. Had regular treatment with hydnocarpus remedies from 1937 to 1944. Became ' negative ' in June 1941, but relapsed in January 1944. Prior to starting of Sulfon-Cilag she had 200 tablets of Diasone which brought on a lepra reaction.

Commenced treatment with Sulfon-Cilag on 25-4-1949 with a bacteriological index of 1.43. Continued treatment regularly till 22nd November '50 except for a break of treatment in January and February 1950, due to lack of supply of the drug. The total dosage of the drug taken was 213.5G. During the course of treatment she had very mild activity in the lesions twice but this cleared up spontaneously. At the end of the therapy, she looked ' much improved ' clinically and her bacteriological index registered a drop to 0.12.

Patient A6. Hindu, male, 34 years. A case of atypical leproma of 10 years' duration. Had routine hydnocarpus treatment irregularly and before starting on Sulfon-Cilag had treatment with Diasone.

Commenced treatment with Sulfon-Cilag on 14-3-1949 with a bacteriological index of 1.56. Continued treatment regularly till

7-7-49 and later stopped away from the treatment. The total amount of the drug administered: 11.0G.

GROUP B:—10cc of Sulfon-Cilag subcutaneously twice a week.

Patient B1. Hindu, male, 20 years. A case of macular leproma of 12 years' duration. Had hydnocarpus treatment irregularly for 12 years.

Commenced treatment with Sulfon-Cilag on 14-3-49 with a bacteriological index of 0.38. Continued treatment regularly till July 1950, when he developed mild lepra reaction. He was given treatment for the reaction and the drug was withheld for two weeks. Restarted treatment on 29-8-50 and continued till 20-11-50. The total amount of the drug administered: 145.5G. At the end of the therapy, the patient appeared ' stationary,' clinically and bacteriological index was 1.25.

Patient B2. Hindu, male, 25 years. A case of moderately advanced leproma of 10 years' standing. Poor vision in both eyes as a result of previous keratitis. Had treatment irregularly with hydnocarpus remedies for 12 years.

Commenced treatment with Sulfon-Cilag on 21-3-49 with a bacteriological index of 2.50. Continued treatment regularly without any untoward sign or symptom till 20-11-50, except for a break of two months in January and February 1950 when the drug ran out of stock. Total amount of the drug administered 149G. At the time the drug was discontinued (November 1950) he appeared ' much improved ' clinically, the infiltration on the face and elsewhere having reduced considerably. The bacteriological index also registered a fall to 0.94.

Patient B3. Hindu, male, 53 years. A case of moderate leproma of over 10 years' duration. Had hydnocarpus treatment regularly for 3 years before starting on Sulfon-Cilag.

Commenced treatment with Sulfon-Cilag on 15-3-1949 with a bacteriological index of 1.75. Continued regularly till 25-3-1949 when he developed lepra reaction. He was given a course of potassium antimony tartrate injections. Improved, but did not turn up for further treatment. He was visited in his house on 19-6-1949 and found to be in a state of severe lepra reaction. It was learnt that he was taking sulphetrone tablets as treatment for the reaction on the advice of a local physician. He was advised to stop the tablets and was given appropriate treatment for his reaction. The reaction later subsided and he was restarted on the same dose of Sulfon-Cilag on 13-10-1949. He went into another mild reaction on 8-12-1949. The drug was then withheld and the patient was treated for the reaction. After the subsidence of reaction he recommenced treatment on 2-3-1950 and continued till 20-11-1950 when the treatment was finally stopped. The total amount of the

SUMMARY OF RESULTS

Case No.	Duration of treatment in months	Total Dosage in Grms.	Complications			Final Assessment	
			L.R.	N	A	Clinical	Bacteriological
A1	18.25	215.0	Nil	Nil	Nil	M.I.	W.
A2	16.75	217.0	Nil	Nil	Nil	M.I.	I.
A3	3.50	41.5	Nil	Severe once	Nil	Not	assessed
A4	12.75	139.5	Severe once	Nil	Nil	M.I.	I.
A5	16.50	213.5	Mild Twice	Nil	Nil	M.I.	M.I.
A6	1.00	11.0	Nil	Nil	Nil	Not	assessed
B1	18.00	145.5	Mild once	Nil	Nil	S.	W.
B2	18.50	149.0	Nil	Nil	Nil	M.I.	M.I.
B3	12.25	95.0	Severe twice, Mild once	Nil	Nil	I.	I.
B4	16.50	132.5	Nil	Nil	Nil	I.	M.I.
C1	14.00	181.5	Nil	Nil	Nil	I.	M.I.
C2	17.25	189.0	Nil	Nil	Nil	I.	N.
C3	16.75	196.0	Nil	Nil	Nil	M.I.	I.
C4	16.75	199.0	Nil	Nil	Mild once	I.	I.

L.R.: Lepra reaction.
N.: Neuritis.
A.: Anaemia.
I.: Improved.

M.I.: Much improved.
S.: Stationary.
W.: Worse.
N.: Negative.

drug administered: 95G. During the period 2-3-1950 to 20-11-1950, the patient once showed mild activity in the lesions. At the end of the therapy the patient appeared slightly ' improved ' clinically the infiltration on the face having subsided somewhat. Bacteriological index came down from 1.75 to 1.5.

Patient B4. Hindu, male, 49 years. A case of early macular leproma of one year duration. Did not have any previous treatment.

Started treatment with Sulfon-Cilag on 25-4-1949 with a bacteriological index of 2.25. Continued treatment regularly till 21-10-1950, except for a period of one month's rest in December 1949. The total quantity of the drug administered: 132.5G. The course of the treatment was uneventful. At the end of the therapy, the patient appeared ' improved ' clinically and the bacteriological index was 0.43.

GROUP C—5cc subcutaneously every day for 6 days in the week.

Patient C1. Indian christian, male, 20 years. A case of moderate diffuse leproma of 7 years' standing. Had hydnocarpus treatment for a year and later resorted to indigenous treatment under which he is said to have had some benefit. Lesions reappeared in November 1948.

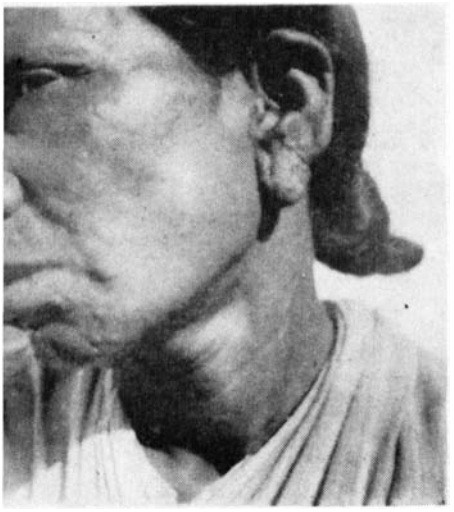
Commenced treatment with Sulfon-Cilag on 16-3-1949 with a bacteriological index of 1.5. Continued treatment regularly till July 1950 when he stopped away from treatment for 3 months due to fracture of his forearm. Recommenced treatment on 6-11-1950 and stopped on 22-11-1950 due to lack of supply of the drug. The total amount of the drug administered: 181.5G. The patient did not develop any untoward symptom during the course of treatment. At the end of the therapy the patient appeared clinically 'improved' and the bacteriological index came down to 0.50.

Patient C2. Hindu, male, 22 years. A case of early leproma of 12 years' duration. Had hydnocarpus treatment irregularly for about 1½ years.

Commenced treatment with Sulfon-Cilag on 17-3-1949 with a bacteriological index of 0.18. Continued treatment regularly up to 22-11-1950 except for a rest period of two months. Total quantity of the drug taken: 189G. The course of treatment was uneventful. At the end of the therapy there was slight clinical improvement: but bacteriologically he became ' negative ' (B.I: 0.00).

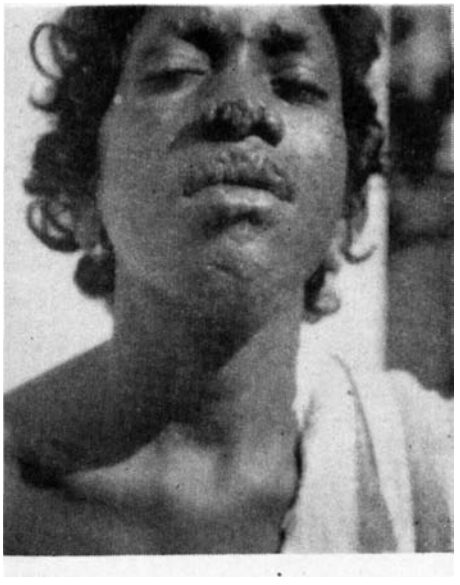
Patient C3. Hindu, male, 40 years. A case of advanced nodular leprosy of 10 years' duration. Had very irregular hydnocarpus therapy.

Commenced treatment with Sulfon-Cilag on 18-4-1949. The bacteriological index being 2.06. Continued treatment regularly till 22-11-1950 except for a rest period of 2 months. The total

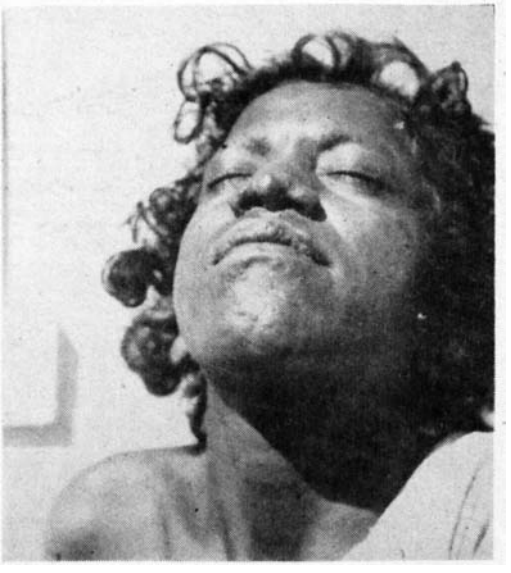


Patient C.3. Before treatment.

Patient C.3. After 10 months' treatment.



Patient A.4. Before treatment.



Patient A.4. After 6 months' treatment.

quantity of the drug taken: 196G. Had an uneventful course of treatment at the end of which he appeared 'much improved' clinically. The bacteriological index at the end of the therapy was 1.62.

Patient C4. Hindu, male, 46 years. A case of moderate leproma of 14 years' duration. Had irregular hydnocarpus treatment.

Commenced therapy with Sulfon-Cilag on 18-4-1949 with a bacteriological index of 2.5. Continued regularly up to 22-11-1950 except for a period of rest for 2 months and an absence of 3 weeks. was uneventful except for the occurrence of mild anaemia in November 1950. At the end of the therapy, the lesions appeared November 1950. At the end of the Therapy, the lesions appeared partly subsided and the bacteriological index was 2.00.

CONCLUSIONS:

1. Sulfon-Cilag appears to be an effective drug in the treatment of leprosy.
2. Administered in appropriate doses it appears to be relatively non-toxic.
3. The intravenous route of therapy does not appear to have any special therapeutic advantage over the subcutaneous route.
4. The subcutaneous route on the other hand, appears to be more effective, considering the results obtained in groups B and C.
5. In group B and C getting the drug bi-weekly and daily, subcutaneously, it is observed that there does not appear to be any appreciable difference in the results. Both appear to be equally effective and hence bi-weekly subcutaneous injections of the drug in doses of 10cc appears to be the method of choice.

SUMMARY

The details of treatment of 14 cases of lepromatous leprosy with Sulfon-Cilag administered parenterally are presented. The results, both clinical and bacteriological, with the complications are recorded.

ACKNOWLEDGMENT

I wish to place on record my sincere thanks to Dr. R. G. Cochrane, M.D., F.R.C.P., the then Honorary Consultant Leprologist, Government of Madras, under whose guidance the investigation was carried out To Cilag Ltd., Switzerland, without whose generous supply of the drug this investigation would not have been possible, grateful thanks are herewith acknowledged. I wish to thank my colleagues, other members of the staff of the Clinic and the patients for their active co-operation.

HUMAN LEPRA BACILLI EXPOSED TO SUNLIGHT WILL RETAIN THEIR ACID FASTNESS IF THEY ARE FIRST HEATED

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In 1949, Dharmendra and Mukerjee (1) showed that when smears of leprosy tissue rich in bacilli were exposed to sunlight, and subsequently stained by the Ziehl-Neelsen method, hardly any bacilli were seen on slides which had been exposed for eighteen hours. Protection of the smears with pieces of black paper prevented the change, which was not therefore due to the heat of the sun. Further tests showed that the ultra-violet rays produced the change but not the infra-red ones—furthermore the sun's rays had no such effect on rat leprosy bacilli.

In 1951 Mukerji (2) was able to produce similar loss of staining ability after five hours exposure to intense sunlight, also after two hours to ultra-violet and infra-red irradiation and after half an hour to X-rays. Smears from rat leprosy were hardly affected by similar treatment, although "beading" was caused in some of them by exposing them to X-rays of 250 r. for twenty-seven minutes.

It had occurred to the present writer that the neuro-ectodermotropism of the human leprosy bacillus as well as its failure to grow on artificial media and possibly certain other of its properties might be due to the parasitization of it by a bacteriophage, bacterial virus, or inhibitory plasmagene, itself harmful in differing degrees to different people.* It is interesting to note that Richards and Wade (3) as a result of their examination of human leprosy bacilli by phase microscopy wrote:—"In examining the preparations from leprosy lesions we gained a general impression of a mixture of rods apparently in good condition but varied in appearance, others in evidently poor condition grading down to apparent residual or ghost bodies, and conspicuous among them and the background debris free, bright granules which could not be dismissed as mere degenerative fragmentation; some of them resembled bacteriophage in general appearance."

It was considered worth while therefore, despite the very limited apparatus at the writer's disposal to see whether the effect of sunlight in causing the human leprosy bacillus to lose its staining properties could be inhibited, and accordingly some pilot experiments were undertaken. It was found for example that when slides

* Dr. Corcos' evidence for this has been placed before workers familiar with the phage phenomenon, and the general conclusions were that such an explanation is unlikely to be correct.—Editor.

were strongly heated, smear side upwards, in the spirit flame until they were too hot to touch, the effect of sunlight on the staining properties (as demonstrated by the numbers of bacilli afterwards seen) appeared to be less than that on unfixed smears; but it was considered that this effect might be relative and partly due to " weathering " i.e. loss of bacilli from the unheated slides from mechanical causes irrespective of their biological state.

It was also found that bacilli which were possible to stain were present, on examination of fixed smears that had been boiled with water *on the slides*, and that these bacilli were still capable of staining after prolonged exposure to sunlight; however this rather crude method was unsatisfactory because it became obvious that boiling for a sufficient length of time to affect the presumed viability of the bacilli might itself be a potent cause of weathering.

According to Stitt, Clough and Branham (4) many bacilli may be lost from a slide if the usual routine of fixation is followed, and for tubercle bacilli these authors recommend that films be passed four or five times through a flame and fixed with absolute methyl or ethyl alcohol. It was considered however that by applying such methods to the lepra bacillus already on the slide it would not be possible to distinguish any possible killing action of the heat or alcohol from their fixative action.

It was eventually decided to compare the effect of sunlight and darkness upon (virtually) unfixed smears of boiled and unboiled leproma tissue from the same patient and the following experiment was therefore devised.

Methods used.

The only available patient at that time was a woman with severe active nodular lepromatous leprosy who had had two years treatment with hydnocarpus oil. She had however had no treatment at all during the two years prior to the present experiment and her skin smears showed enormous numbers of normally staining bacilli and globi.

From both ears of this patient nodules of approximately the same size were removed. That from the right ear was untreated and smears were made from it directly on to one end of each of fourteen clean microscopic slides which were allowed to dry in the shade, while the nodule from the left ear was boiled for half an hour in distilled water, as for the first stage of making lepromin. The water was poured off and smears were made from the boiled nodule on to the other ends of the slides. All the slides were now drawn *once* rapidly over the flame of a spirit lamp so that they became only just warm to the back of the hand.

Seven of the slides were then exposed to bright sunlight for a total of 24 hours on three successive days while the other seven were kept in a closed slide box except for 20 hours during two dark nights when the slide box was left outdoors with the lid open. Altogether the exposed slides had 24 hours of sunlight and approximately 29 hours in the dark in a closed slide box, while the unexposed slides were in the dark for 53 hours before being stained and examined.

In order to reduce the possibility of acid-fast saprophytic mycobacteria from the materials and apparatus used being mistaken for leprosy bacilli six blank sides were treated with distilled water from the same bottle that contained the water used for boiling the leproma tissue; the water was allowed to evaporate from the slides in the shade and three of them were then placed with the exposed slides, while three were placed with the unexposed ones. They were stained and examined at the same time and by the same methods as the experimental slides.

Immediately prior to examination all the slides were drawn four times through a flame, treated with absolute methyl alcohol and again flamed. They were stained by the Ziehl-Neelsen hot method, decolourized with 5% sulphuric acid and counterstained with methylene blue, a slide rack being used and care being taken to give all slides equal times in carbol fuchsin, acid and counterstain. They were then stood on end on a grooved board and allowed to dry—they were not blotted. Each smear was now carefully examined with the 1/12 oil immersion objective, using first the X5 and then the X12 eyepiece and the scheme shown is used to express the results:—

+ + + + + +—Vast numbers of bacilli in all fields examined.
+ + + + + —Vast numbers of bacilli in 50% of fields examined, large numbers in the other 50%.
+ + + + —Large numbers of bacilli in all fields examined.
+ + + —Large numbers of bacilli in 50% of fields examined. fewer bacilli or none in the other 50%.
+ + —Some bacilli in 50% of fields examined.
+ —Some bacilli in 10% or less of fields examined.
± —Single scattered bacilli present in smear, only identified with difficulty.
– —No bacilli seen.
G—Globi.

(Presence or absence of globi could not be taken into account in expressing bacillary density since it was found that in the smears of the boiled leproma all globi had been broken up and the bacilli

were scattered unevenly about, and, for example smear " Dark—Boiled I." contained vast numbers of bacilli but no globi, whereas smear " Dark—Untreated 3." contained fewer bacilli but some globi.)

	EXPOSED.		DARK.	
	Untreated leproma.	Boiled leproma.	Untreated leproma.	Boiled leproma.
1.	... −	+ + + +	+ + + + G	+ + + + + +
2.	... ±	+ + +	+ + G	+ + + + + +
3.	... −	+ + +	+ + G	+ + + + + +
4.	... ±	+ + + + +	+ + + G	+ + + + +
5.	... ±	+ + + + + +	+ + + + + G	+ + + +
6.	... +	+ + + + +	+ + + + G	+ + + +
7.	... ±	+ + + + + +	+ + + + + G	+ + + + +
	BLANK.		BLANK.	
1.	...	−	−	
2.	...	−	−	
3.	...	−	−	

Discussion of Results.

These results appear to confirm those of Dharmendra and Mukerjee but go rather further in that they seem to show that heating of human leprosy bacilli by boiling them " protects " them from the effect of sunlight. The situation at present then, seems to be that the actinic rays could in theory either be disintergrating the bacilli or be merely rendering them resistant to ordinary staining methods; the point might later be decided by dark-ground, electron microscopy and phase contrast microscopy methods. It is hoped that others will be able to repeat and extend these irradiation experiments, for example, it would be particularly interesting to know what, if any, effect ultra-violet light and X-rays have upon chloroform treated bacilli.

The present writer hopes to undertake further work in order to try and find out for how long boiled lepra bacilli can be exposed to sunlight without losing their acid-fastness. If as he believes, sunlight only affects the staining properties of the living bacilli but not those of dead ones, it should be possible to expose heated bacilli more or less indefinitely without their losing their ability to stain, and some preliminary experiments already strongly suggest that such is indeed the case.

Summary.

The effects of sunlight and darkness upon smears made from boiled and unboiled leproma tissue taken from the same patient are compared. Reasons are given why the results obtained were to be expected.

Acknowledgment.

Permission from the Inspector General of Medical Services, Nigeria to publish this paper is acknowledged with thanks.

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To The Editor, 7th March, 1953.
Leprosy Review.

PENICILLIN AND PERFORATED ULCER.

One of my European patients, who was under my care at Ngomahuru in S. Rhodesia, for some 3 years, developed a perforated ulcer of the sole of the right foot, after returning to his home in Kenya, where he again came under my supervision.

The microscope failed on several occasions to reveal any M. Leprae, but the ulcer persisted for months, discharging yellow pus, packed with staphylococci.

I had given the patient Penicillin injections on various occasions, and he had always remarked that they had done him a great deal of good, so, a determined effort was made, and he received one million units of crystalline Penicillin G. Sodium salt, intramuscularly, every day for ten days, at the end of which time the ulcer had completely healed.

The result is a remarkable change in the psychology and ambulatory powers of the patient. He is free from pain, and can now get about his farm on horseback or by car in complete comfort.

No doubt, the Penicillin was responsible for the demise of the cocci, which had been the real cause of the persistence of the ulcer.

Perhaps you can see your way to publish this in the " Review."

B. MOISER
(Late Leprologist to Govt. of S. Rhodesia).

REVIEWS.

Leprosy in India, Vol. 24, No. 3, (July, 1952).

Thiosemicarbazone in the Treatment of Leprosy by Dharmendra and Chatterji, K. R.

After reviewing the previous literature on this subject, an account is given of the results of treatment in 52 cases. Nine of these were untreated neural cases; 27 were untreated lepromatous cases; 15 were lepromatous cases previously treated with sulphones; had been previously treated with hydnocarpus oil. Treatment with the siocarbazone brand of thiosemicarbazone averaged 10 months. The most remarkable feature of the results was that, in addition to the usual therapeutic effects, there was complete or partial restoration of sensation in the anaesthetic patches and in the limbs with the polyneuritic type of anaesthesia, replacement of diseased nails by new ones, and growth of new hair in depilated areas, remarkable considering the short term of treatment. In general the toxicity of thiosemicarbazone seems to be less than that of the sulphones. However " a special kind of toxicity which indicates specific intolerance has been noticed and this has been manifested by a sudden rise of temperature even after small doses of the drug." The dose recommended is 25 mgm. gradually rising to 200 mgm. per day. It is found particularly useful in patients who cannot tolerate sulphones, or who cease to progress under treatment with sulphones after an initial improvement.

Thirty-five Years of Vasectomy by Mitsuda, K.

This method is strongly advocated by the author so as to make it possible for male and female leprosy patients to live together without having children. The patients are thus able to live a more normal and happy life without having children who fall an easy prey to leprosy. During the last 20 years the author has performed the operation of vasectomy successfully in 652 patients. He found that there was no change in the secondary sexual characters, nor was there any decrease of sexual desire. The method advised is very simple, the vas being located on the postero-lateral side of the scrotum, and each operation taking only 5 minutes under local anaesthesia (procaine). " The double folds of skin are then penetrated with a needle, so as to fix the vas deferens between the needle and the skin layer. It is left in this position till the operation is finished. An incision 0.5 to 1.0 cm. long is made in the overlying skin and then through the fascial layers. The thick white vas deferens is exposed and pulled out for a length of 3 cm. with a pair of forceps, taking care not to damage the accompanying blood

vessels. It is then ligated in two places, and 1.5 to 2 cm. length of it between the two ligatures is excised." The same process is carried out on the other side.

Diaminodiphenyl sulphone in Leprosy by Roy, A. T.

A comparison is made between the oral and the parenteral methods of administering DDS. Of the 98 oral cases, treated for an average period of 17.1 months, there was improvement in 75 per cent. Of the 140 parenteral cases, treated over an average period of 12 months, there was improvement of 74.2 per cent. The average amount of DDS per patient for 12 months in the former was 28.5 gm., and for the latter only 19.38 gm. The author concludes: " If the trouble of injecting the suspension is not taken into consideration, there is a great advantage in using the suspension of DDS parenterally. Here both the amount of the drug and the period of treatment are lessened to a great extent." [There is a possibility that the conclusion of the author is right, and that parenteral administration of DDS is more quickly effective than oral. If so, this may be the result not of more efficient absorption of sulphone but of the counter-irritant effect of the injections increasing the effects of the sulphone. There appears however to be a possible fallacy in the author's reasoning. The average amount given orally per patient per year was 28.5 gm., which works out at 548 mgm. per week. There is evidence that 600 mgm. orally per week may give as good results as larger doses; but many of the 98 cases were not able during long periods to stand as much as 548 mgm. per week, and yet they improved considerably, whereas others got far greater doses, many of them 1200 mgm. and some even 1800 mgm., amount which further experience indicates possess little, if any, advantage over 600 or 800 mgm. per week.]

E. MUIR.

" The Mask of a Lion," by A. T. W. Simeons. Victor Gollancz. 12/6d.

Many books on leprosy are written from the angle of pity and compassion and tend to overemphasis in this direction. On reading this book for the second time one could not but be convinced of the writer's honesty, sincerity and accuracy. Dr. Simeons writes with a deep and understanding sympathy of the afflicted " Brotherhood " and gives a vivid picture of the plight into which his hero is precipitated by the discovery of his condition.

Here is laid before us the physical, mental and spiritual reaction of the leprosy patient, which, although set in this instance in the customs and background of Hindu India, must be essentially similar in every sufferer. The triumph of faith is in this case

brought to a happy conclusion by the equal victory of new therapy over the disease.

It is to be hoped that as research data permits, the author will give us a sequel further emphasising the modern, enlightened approach to leprosy, and leading to the banishment of fear on the part of the public. The cause of leprosy would be much advanced if he could indicate those measures, both surgical and occupational, available for the patient's rehabilitation, and also those which will vitally assist in the control of the disease, both in the laboratory and in the field. E.B.

Cochrane, R. G. *Leprosy—with particular reference to conditions at present pertaining in the British Isles.* Public Health (1952) Sept.

In this address to the Medical Officers of Health of London the writer has endeavoured to remove many fears and prejudices which unfortunately still persist not only amongst lay people but also amongst doctors.

Since leprosy was made notifiable in 1952 about 100 cases of leprosy have been notified in England and Wales. Possibly a further 50 cases may remain unnotified or unrecognised. No case has been traced to infection from a patient in Britain. A new attitude towards leprosy needs to be encouraged by education and by the avoidance of the use of the words " leper " and " unclean " by doctors. Finally the writer spoke of the facilities for treating leprosy in England and regretted the local opposition to the new hospital at Redhill, Surrey.

Cochrane, R. G. *Four Cases illustrating aspects of leprosy.* Proc. Roy. Soc. Med. **45** (1952) No. 5. p. 249-253.

Two typical tuberculoid cases, one atypical lepride, and one advanced lepromatous case were demonstrated. X-ray photos of a further lepromatous case were shown which revealed considerable rarefaction of the phalanges and absorption and necrosis of the metatarsal bones.

One of the tuberculoid cases—a boy—had had nerve decompression of his left ulnar, and the atypical cases had had both his peroneal nerves decompressed with great relief.

Surprise was expressed by those present that the writer handled the patients and that the boy was allowed to go to school. He explained that the disease was very mildly pathogenic and healthy adults were relatively non-susceptible and that the lesions in the boy were quiescent and not in any way infective.

G. O. TEICHMANN.