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EDITORIAL

THE TREATMENT OF LEPROSY AND THE TREATMENT OF TUBERCULOSIS.

There was a time when leprosy and tuberculosis were considered as two entirely unrelated diseases, different in every respect except perhaps in chronicity.

When the two organisms were discovered (and the discovery of the leprosy bacillus came first, and possibly led to the discovery of the tubercle bacillus, for Koch was undoubtedly influenced by the work of Hansen) the similarity of the two organisms was recognised. More than 20 years later certain histopathological relationships were recognised, and these led to our present use of the term tuberculoid leprosy.

During the last two decades two new factors have appeared. Studies by several workers, particularly Fernandez in the Argentine, have shown that there is some immunological relationship between the two infections. Further, chemotherapeutic studies in vitro, in animals, and in man, showed that sulphones had some activity against the tubercle bacillus in vitro and in animals, and also against the leprosy bacillus in man. Thus, some chemotherapeutic relationship between these two infections has become recognised.

Studies with sulphones against the leprosy bacillus in vitro and in animals were ruled out by the failure to cultivate or to infect animals with the leprosy bacillus. Studies of sulphones in human tuberculosis did not give clear cut results, and the studies were cut short by the advent of streptomycin and later P.A.S. thiosemicarbazone and isoniazid.

But it has never been clearly shown that sulphones have no real value in the treatment of tuberculosis, although it is clear that other agents, particularly streptomycin and isoniazid are much more active. It is possible that sulphone is as active as P.A.S., or even as thiosemicarbazone, in tuberculosis. Moreover, it has been shown that sulphones possess (but to what extent is not clear) the important property of P.A.S., namely, that when given in combination with streptomycin, the development of streptomycin resistance in the tubercle bacillus is delayed.

Of the therapeutic agents mentioned, thiosemicarbazone is little used in tuberculosis because of toxicity, and sulphone is little used for lack of real evidence of its value. Streptomycin and isoniazid remain in use because of their marked activity until drug resistance develops, and P.A.S. remains in use as a method of delaying this resistance.

But sulphone should not be entirely forgotten as a possible chemotherapeutic agent in diseases other than leprosy. Sulphones have their main function in the treatment of leprosy, but they may also have their wider uses, and it is the leprosy worker who may be able to give evidence on this matter.

Patients suffering from leprosy frequently suffer from other infections, and a very common one is tuberculosis. Is it the experience of physicians treating leprosy that sulphone is of value in the treatment of tuberculosis occurring in their leprosy patients?

On this question there are available four pieces of evidence. The first is the report of Gray and Bancroft, (1952) (*Internat. Jour. of Lep.* **20** p. 463), from the National Leprosarium, Carville, Louisiana, U.S.A., where sulphone treatment of leprosy was first used. These workers state, and give strong evidence to support their statement, that since sulphone treatment of leprosy became general in their institution the incidence and the mortality of tuberculosis among their patients has fallen markedly and steadily; they attribute this to the effect of sulphones on tuberculosis infection.

The Editor, in 6½ years' experience of treating leprosy in Nigeria, came to the same conclusion, that the routine use of sulphone treatment of leprosy had produced a definite fall in the incidence, severity and mortality from tuberculosis among his patients. This matter is referred to briefly in an article in the present issue.

In our present issue we also publish a report by Dr. C. J. Austin of findings in the leprosarium in Fiji in which he reports similar findings, and also stresses the great value of isoniazid in the treatment of tuberculosis in his patients.

Our fourth report on this matter is also contained in this present issue in an article by Dr. Relvich, based on experience in West Nigeria. His report states that he has seen no evidence that the sulphone treatment of leprosy has reduced either the incidence or the severity of tuberculosis among his patients.

Thus, of the four witnesses when asked " Does sulphone treatment have a favourable effect on tuberculosis in leprosy patients?, three answered yes, and one answered no.

The Editor, being a witness of one side in this matter, cannot claim to judge the matter quite impartially, but he thinks that the evidence for the favourable action of sulphone in tuberculosis is very strong. In all the three favourable reports the patients were under close medical supervision for a period of several or many years; in the one unfavourable report the patients were in outstations, with much less close supervision, and the experience reported is considerably shorter.

If it is accepted that sulphones exert a favourable effect on tuberculosis, we must try to go further and say how this effect is brought about. The findings reported could be explained on the basis that sulphones exert a suppressive action on tuberculous infection; that in patients with latent infection, the infection is kept latent; that in patients with patent infections, the progress of the disease is arrested or slowed down. These ideas would be in accord with the Editor's personal experience in Nigeria in the treatment of tuberculosis in leprosy patients. His findings were briefly as follows. Sulphone given alone as a treatment for patent tuberculosis gives disappointing results; in very few cases is the disease arrested, although its progress may be slowed down. The combination of sulphone with either or both of the more active agents, streptomycin and isoniazid, has given much better results. In some cases, arrest of the disease has been produced; in other cases the acute disease has been controlled, and the disease has been rendered mild and chronic; definite clinical indications of the tubercle bacillus having become resistant to treatment have not been marked, but unfortunately tests of drug resistance have not been possible.

Thus the role of sulphones in the treatment of tuberculosis might possibly be that now allotted to P.A.S.—a minor but an important one; its own action on the infection is slight, but it enables the other agents, streptomycin and isoniazid, to act more effectively and for a longer time. It should be mentioned that sulphone is much cheaper and easier to give and to take than is P.A.S., the dose being 1-200 mgm a day of Dapsone, instead of 15,000-20,000 mgm a day of P.A.S.

In the Editor's experience in Nigeria, tuberculosis of the lungs can often be treated successfully with these three drugs, streptomycin, isoniazid and sulphone. Isoniazid and sulphone can be given every day for very long periods, and in addition streptomycin should be given when it is indicated, and for as long as it is advisable or possible. One or more courses of at least several weeks' duration are often of great value, and administration may be every other day and not daily.

The Editor's experience of thiosemicarbazone in the treatment of tuberculosis in Africans has not been as favourable as reported by Dr. Relvich, and he prefers the therapeutic agents mentioned above.

In our present issue we abstract a report on the value of isoniazid in the treatment of tuberculosis in African children, which may be of general interest.

MODERN LEPROSY TREATMENT.*

By DR. C. J. AUSTIN, O.B.E.

THE PRESENT POSITION OF LEPROSY TREATMENT

On being asked by your assiduous Secretary to give you an "up-to-date" assessment of the results of the modern treatment of leprosy, I immediately sent off an SOS to Makogai for the latest information, for in these days of rapid change I already feel something of a back number, although it is only about six months since I left the Islands.

From the information received, however, it does not appear that there has been any spectacular progress in the interval, but it is a great satisfaction to hear that so many whom one had seen starting on the upward path are continuing to improve.

As a general background, it may be of interest to note that the average daily number of patients at Makogai last year was just under 700, of whom approximately 58% were from Fiji, and 42% from beyond the Colony—i.e. from Samoa, Tonga, the Cook, Niue or Gilbert Islands. This represents the lowest figure for Fiji itself since 1938, but is partly explained by the fact that patients are now retained under supervision at Makogai for one year only, instead of the previous two years, from the time they cease to show activity of their disease. I think we may definitely regard this as a step in the right direction, both as an indication of our confidence in modern treatment, and as a tribute to the adequacy of the follow-up service, by which discharged patients are traced and examined at regular intervals.

Fifty-seven patients were discharged during 1952, of whom 41 were Fiji residents and only 16 from overseas, but here again it is necessary to point out that this large preponderance of patients from Fiji is due, in part at least, to the fact that until this year Fiji alone had reduced the period of surveillance at Makogai. This change-over has now been adopted by the other administrations, and 57 patients have already been discharged from Makogai this year, of which number 31 were from Fiji and 26 from beyond the Colony. The latter figure includes 10 from the Cook Islands, 8 from Samoa, 6 from the Gilberts and 2 from Tonga. On the whole the change in Regulations is likely to affect the Cook Island patients,

*A paper originally presented at the Second Leprosy Trust Board Conference, Christchurch, New Zealand, September, 1953.

the majority of whom are early cases, to a much greater extent than the Samoan and Gilbert Island people, who have a larger proportion of the more advanced cases.

Mortality last year was remarkable in two ways—firstly, in that there were only thirteen deaths, the lowest number since 1920, when the sick population was about one-third of the present total: and secondly, in that it included no deaths from tuberculosis which has always been regarded as one of the important causes of death in leprosy patients. I think there is no doubt we can attribute both of these improvements very largely to the effects of modern therapy, although, as the certified causes of death showed that nine of the 13 deaths were directly or indirectly due to leprosy itself, it is evident that we still had a hard core of advanced cases beyond the power of any drug so far tried, to ameliorate. This is not surprising, for although in the great majority of cases the organism of leprosy directly attacks only skin and nerves, the continual excretion over a number of years, of the toxins produced by the disease, naturally results in such a degree of degeneration of the essential tissues of the kidneys, liver, and intestines, that these organs are rendered almost functionless, and the body is thus shorn of its main defences.

That this low death rate for 1952 is more than a chance figure is supported by the fact that up to the middle of August of this year —a period of 7½ months—there have been only six deaths. I have no information as to whether these deaths included any attributed to tuberculosis.

With general reference to the latter disease, our results serve to endorse your conclusion that leprosy cannot be successfully attacked as a separate entity, and your consequent policy of regarding the struggle against leprosy as part of a general medical programme. In my paper to your first Conference, I remarked that " as a poor relation of Tuberculosis, which being widely spread among the more affluent populations of the world, has more money and attention devoted to it, leprosy is sometimes able to benefit from the crumbs that fall from the rich man's table," and I added that " the Sulphone drugs may be regarded as among such crumbs " for they had been first tried out in tuberculosis. To the sulphones I would now add the thiosemicarbazones, isonicotinic hydrazide and streptomycin. These drugs not only appear to have a beneficial effect on leprosy itself, but naturally help us greatly in its tuberculosis complications.

At the end of last year, I was able to record that although we had 23 certified cases of tuberculosis, only 6 of these had required treatment for active disease during the year, the disease having been rendered quiescent in 17 patients who had therefore

been enabled to return to their respective villages at Makogai for treatment of their residual leprosy. In the same report, I spoke of Pycazide—a form of isonicotinic hydrazide—as " having been given to patients in more advanced stages, most of whom had failed to improve under, or even to tolerate, other drugs. Fourteen of the sixteen in this series had been subject to constant or frequent lepromatous reactions, which in some cases resulted in actual ulceration. In all but one of the reactionary cases, the reactions either ceased or were greatly diminished under Pycazide. In the one exception, the ulceration cleared in spite of the fact that reactionary fever continued. Three of the patients, including the last mentioned, were also suffering from pulmonary tuberculosis, accompanied in one case by tuberculosis of the spine and in another by ischio-rectal abscesses. The two latter patients were regarded as moribund, but both have become apyrexial, and each has put on more than a stone in weight."

The one referred to as having ischio-rectal abscesses—a young Gilbert Island boy—deserves a note on his own. He was not only suffering from almost constant lepromatous reaction, but his x-ray picture showed what can only be described as a " shower " of tuberculous shadows involving the whole of both lungs, but especially heavy in the right sub-apical region. In the process of clearing, this latter area developed a mass of fibrous tissue, which, by contracting, pulled the whole heart over to its own side, so that practically the whole of the cardiac shadow could be seen to the right of the sternum instead of to the left. It is not surprising, therefore, that his convalescence was attended by sundry fainting episodes in the process of attempted accommodation to the new cardiac position, and it is a relief to know from recent reports that he is continuing to do well.

Before leaving the subject of tuberculosis, I may perhaps refer to the " bad old days " prior to your gift of the x-ray plant, when our impression was—and this was fairly general throughout the Colony of Fiji—that our Islanders were particularly susceptible to tuberculosis, and that once they had it, their chances of surviving more than a few months were very slender. It was only gradually that we began to realise we were failing to recognise anything but the advanced stages. Since then, an x-ray survey of all tuberculin-sensitive patients and of all fresh admissions has enabled us to diagnose and treat the earlier stages which are so eminently favourable. Now that we also have more potent drugs, tuberculosis should soon cease to be the dread complication that it has proved in the past, especially as by treating leprosy with these drugs, which may be regarded as dual-purposive, we may well be nipping incipient

tuberculous infections in the bud, before they can become clinically recognisable. Most Makogai patients are taking some form of sulphone treatment and many are still on Sulphetrone, the drug with which we started our sulphone trials at Makogai. Ten patients in fairly advanced stages of leprosy, with reactionary ulceration, who were unable to tolerate sulphones in any ordinary dosage, have improved considerably on intramuscular injections of 25 or 50 mg. of Sulphetrone, which, being only about 1/60 of the normal dose, might well have been thought too ridiculously small a dosage to have any effect whatever. Nevertheless lepromatous ulcerations of skin and throat have cleared under this regime when all else had failed.

Sulphetrone is, however, a proprietary drug, and as such, necessarily more expensive than its basic principles—diamino-diphenyl-sulphone—from which it is built up—and to which it breaks down in the body. Diamino-diphenyl-sulphone—DADPS, DDS, or Dapsone—as it is now variously called—was originally considered too toxic for human use, but has since proved equally effective, in very much smaller dosage, with Sulphetrone or any other of the proprietary sulphones. On grounds of economy, therefore, as well, perhaps, as of safety, it is steadily replacing the proprietaries in most leprosaria.

Experimental work is still proceeding with several other drugs —notably the thiosemicarbazones, as represented by Thiacetazone and Ethizone; and isonicotinic hydrazide or Isoniazid, as it is now officially termed, as represented by Pycazide and Cotinazin. To quote from my report on Thiacetazone—" of 27 patients who had proved intolerant to sulphones (16 constant severe reactions, 8 with psychotic manifestations, and 3 with drug rash), 10 were recorded as ' Much Improved,' 10 as ' Improved ' and 7 as ' Stationary '; and regarding Ethizone 9 ' The results in those intolerant to sulphones are definitely encouraging.'' Summing up, I added—" It does not, therefore, appear to me from these results that the thiosemicarbazones are likely to supplant the sulphones, but they may well prove a very useful auxiliary, either as part of a combined treatment, or as a substitute in cases where patients are unable to tolerate the sulphones.

Regarding the Pycazide form of isonicotinic hydrazide I have already quoted from my report, but with Cotinazin, which we tried on earlier cases of leprosy, we had less success, though this did not seem to be due to any difference between the two drugs, and I concluded my report with the view that Isoniazid appeared to be more effective in the advanced stages of leprosy, and particularly in patients with frequent reactions. I now understand that a roughly

similar view has been taken of results from Isoniazid in tuberculosis.

A small series of ten patients were put on a Dublin product—B 283, or, if you will, 2 anilino—3 amino—5 phenylphenazide hydrochloride—which had been lauded in Nigeria for its efficacy and for its superiority over the sulphones in the treatment of leprosy. Seven of the ten patients showed about the same degree of improvement as would have been expected with the Sulphones: one patient seemed worse, and two remained about the same. This is much too small and short a test, and if a further supply of the drug can be obtained, we shall await the results of an extended test with interest.

Taking an overall picture of last year's results at Makogai—of 704 patients reported on, 217 had become Inactive and 283 were graded as Improved; 155 were recorded as Stationary, but many of these had already been upgraded—e.g. from Lepromatous 2 to Lepromatous 1—so that it would have required a high degree of improvement to be recorded. 36 were regarded as Worse, and I have already alluded to, and commented on, the 13 deaths.

A few years ago, these results would have been considered remarkable, as indeed they would have been—and it is a tribute to present-day treatment that we take them for granted, and even think that the number recorded as Stationary calls for an explanation. With the small doses of sulphones now employed, fewer patients prove intolerant, but we are extremely fortunate that other drugs, such as the thiosemicarbazones and isonicotinic hydrazide, are now available for the comparatively few cases completely recalcitrant to the sulphones.

I cannot, however, too often emphasise that drugs, however efficacious, are still by no means the only factor in treatment. I have briefly referred to the effect on the tuberculosis aspect, and consequently on the whole leprosy situation at Makogai, of your gift of an x-ray plant some years ago. Electro-therapeutic equipment is virtually, if not literally, on the way, and judging by the personal reports received from New Caledonia, will do much to alleviate pain, and prevent or repair deformities. Your never-failing generosity in all directions continues to bring physical and psychological uplift to sufferers—not only at Makogai, but throughout the South Pacific—and offers the firmest of foundations on which modern drugs can play their essential part in building up disease-resistant bodies.

THE TREATMENT OF TUBERCULOSIS IN LEPROSY PATIENTS

A. L. RELVICH, M.D., D.T.M. and H.
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Tuberculosis is a fairly frequent complication of leprosy, particularly in lepromin-negative lepromatous cases, and is often a direct cause of death in this disease. For instance Gray and Bancroft (1952) attribute to it 21.7% of deaths at Carville Hospital in the pre-sulphone era. Similar figures have been reported by other workers.

The following observations have been made on treatment of tuberculosis in leprous patients in Ossiomo Settlement in Nigeria. In 1945 this settlement became the centre of leprosy control of the Benin and Delta provinces in Western Nigeria. Segregation villages were established in these two provinces, and, as more and more patients came under the medical supervision of the staff of Ossiomo Settlement, more and more cases of tuberculosis were diagnosed. Naturally with two medical officers in charge of a fluctuating population of about 5000 patients, and with no X-ray facilities, it has been impossible to diagnose early cases. Only when a patient had been noticed to be losing weight at an abnormal rate or to have a constant rise in temperature or persistent cough, he was examined by the touring Medical Officer and his sputum tested for acid fast bacilli. If tuberculosis had been diagnosed, the patient was transferred to the settlement and segregated there in an isolation ward. He continued receiving the anti-leprosy treatment, and, in addition, a diet rich in proteins and vitamin preparations. The mortality rate was very high, and few of these patients survived. In the five years between 1947 and 1951, tuberculosis of lungs was diagnosed in 50 patients out of whom 45 have died. Sulphone treatment was introduced in this area gradually in 1950 and early in 1951. Unlike Carville Hospital, there has been no appreciable improvement, here, as far as tuberculosis is concerned. There might have been a decrease in morbidity difficult at present to assess because of the increase of the number of patients owing to the simultaneous increase in the number of segregation villages. There has been no change whatever in case mortality.

Improvement in this situation came for the first time with the introduction in January 1952 of thiosemicarbazone as a routine treatment for our patients with tuberculosis. Out of 16 patients who received that treatment until September 1953 only three have

died. However, only in one of these patients sputum has been rendered free of acid fast bacilli and all physical signs of involvement of lungs have disappeared.

In March 1953 the report of the Medical Research Council Committee on chemotherapy of tuberculosis with streptomycin, para-aminosalicylic acid and isoniazid appeared and showed most encouraging results. This treatment is naturally expensive, but we decided that we could afford to give it a trial on the regimen of 1 gram of streptomycin on alternate days. It was thought also that it would be interesting to evaluate at the same opportunity the influence of these drugs on leprosy.

The reports in the literature on the effect of treatment of leprosy with these drugs are rather conflicting. Erickson (1951) considers streptomycin as useful in combination with sulphones for hastening the resolution of lesions when these have reached a stationary stage. He found that in the dosage of 1 gram daily streptomycin appears to have a suppressive effect upon leprous lesions, but its toxicity precludes continuous administration beyond a period of 6-9 months. Gonzalez Ochoa (1952) found dihydrostreptomycin to be inferior to DDS. On the other hand Garolmo (1953) reports that out of 6 lepromatous cases treated with dihydrostreptomycin, 5 became bacteriologically negative with complete regression of skin symptoms in 14 months.

As far as treatment with isoniazid is concerned, Torrello (1952) reported great improvement after treatment of lepromatous cases for nine weeks. Secret (1952) reports considerable improvement in his patients after few months' treatment; so do Lippi and Tucci (1953). Latapi and co-workers (1953) found isoniazid therapeutically active in lepromatous leprosy. On the other hand Lowe (1952) found that isoniazid may be of slight benefit but its action is much less than that of sulphones or thiosemicarbazone. Dharmendra and Chatterjee (1954) report isoniazid to be of definite value in the first 8-12 weeks, but on the whole not very effective since there is usually a setback in the initial improvement. Jopling and Ridley (1954) treated eight patients suffering from lepromatous leprosy for six months and did not find definite clinical or bacteriological evidence of improvement.

OUTLINE OF THE TRIAL.

The present trial was undertaken chiefly from the point of view of treatment of tuberculosis. Very few of the patients would have been selected if the main purpose were evaluation of the action of drugs on leprosy. Nevertheless it was thought that some useful results might be gained also in this direction.

The treatment was started in September 1953. In that month, 13 patients who had been treated with thiosemicarbazone for 9-20 months were put on streptomycin and isoniazid. All these patients had symptoms of active open tuberculosis of lungs. Five more patients were added to the trial later. In three of them, tuberculosis of lungs had been diagnosed, in one tuberculosis lymphadenitis, and one was suspected of having tuberculosis laryngitis. They have been all receiving intramuscular injections of 1 gram of streptomycin on alternate days, and 100mg of isoniazid twice daily. Both drugs were given continuously. Two patients in whom acid-fast bacilli did not disappear from the sputum in four to five months were changed from streptomycin to para-aminosalicylic acid 20 grams daily, while isoniazid was continued in the same dosage. It was thought that their tubercle bacilli might have become resistant to streptomycin. The patients were weighed every month and their sputum tested for acid-fast bacilli. They were examined in three-monthly intervals from the point of view of leprosy (bacteriological smears and clinical examination). Unfortunately it has not been possible to have X-ray examinations and to culture their bacilli and test them from the point of view of acquired resistance to the drugs. The trial was ended in June 1954.

CLINICAL OBSERVATIONS.

Case 1. Male, aged 30. Admitted to the settlement in 1938 with lepromatous leprosy. Since 1950 has been on sulphone treatment. In September 1952, acid-fast bacilli were found in sputum and treatment was changed to thiosemicarbazone. In September 1953, streptomycin and isoniazid started. Acid-fast bacilli disappeared from sputum by December 1953; weight increased from 126 lbs. to 140 lbs. At the beginning of trial, clinical signs of active leprosy had gone but smears were bacteriologically positive (less than 10 bacilli in the field). At the end of trial in June 1954, they were reduced to about one bacillus in the field.

Case 2. Male, aged 50. Admitted in 1936 with tuberculoid leprosy. Since 1950 on sulphone treatment. Tuberculosis of lungs was diagnosed in March 1952, and he was put on thiosemicarbazone. In September 1953 he was put on present trial. Acid-fast bacilli disappeared from the sputum by December 1953. Weight increased from 112 lbs. to 126 lbs. There were no signs of leprosy left at the beginning of the present trial, and as the patient did not show any signs of active tuberculosis, he was discharged symptom free in May 1954.

Case 3. Male, aged 25. Admitted in May 1953 to a segregation village with lepromatous leprosy and put on DDS treatment. In September 1953 he developed high temperature with symptoms and signs of pneumonia. As there was no improvement with penicillin treatment, his sputum was tested and found to be very positive for acid-fast bacilli. He was put on streptomycin and isoniazid. In two weeks his temperature settled to normal. Sputum became free of acid-fast bacilli by December 1953. Weight increased from 113 lbs. to 154 lbs. No clinical or bacteriological improvement has been observed as far as leprosy is concerned.

Case 4. Male, aged 45. Admitted in 1950 with lepromatous leprosy and put on DDS treatment. In June 1951 he was found to be suffering from open tuberculosis of lungs, and in January 1952 his treatment was changed to thiosemicarbazone. Put on streptomycin and isoniazid in

September 1953. Acid-fast bacilli in the sputum, already scanty, disappeared by the next month. Weight increased by four pounds. Altogether his tuberculous infection, never serious, was probably nearly cured at the beginning of the trial. Slight bacteriological improvement as far as leprosy is concerned, but none clinical.

Case 5. Male, aged 30. Admitted in 1945 with lepromatous leprosy. Sulphone treatment started in 1950. Open tuberculosis of lungs diagnosed in June 1949. Thiosemicarbazone from April 1952. In September 1953, put on present trial. Acid-fast bacilli disappeared from sputum by November 1953, weight increased from 134 lbs. to 165 lbs. The patient was bacteriologically positive for leprosy at the beginning of the trial but there were no clinical signs of leprosy. His smears became negative by March 1954.

Case 6. Male, aged 45. Admitted in 1948 with lepromatous leprosy. Sulphones in 1950. Acid-fast bacilli found in sputum in July 1951. In March 1952 transferred to thiosemicarbazone. Put on present trial in September 1953. Acid-fast bacilli disappeared from the sputum by November 1953, weight increased from 115 lbs. to 124 lbs. There were no clinical signs of active leprosy left at the beginning of the trial. Scanty bacilli in smears disappeared by March, 1954.

Case 7. Male, aged 25. Admitted in June 1950 to a segregation village with tuberculoid leprosy. In October 1951, open tuberculosis of lungs was diagnosed, and the patient was transferred to the settlement. In March 1952 he was put on thiosemicarbazone. In September 1953 put on the present trial. Acid-fast bacilli disappeared from sputum by November 1953; weight increased from 112 lbs. to 118 lbs. He had no signs of leprosy left at the beginning of the trial. All clinical signs of tuberculosis of lungs have disappeared, and he was discharged symptom free in May 1954.

Case 8. Male, aged 25. Admitted to a segregation village in 1948. On DDS since April 1951. Open tuberculosis of lungs diagnosed in June 1952. He was transferred to the settlement and put on thiosemicarbazone. His temperature has been rising persistently up to 100° in the evenings, and the general condition has been obviously deteriorating. Put on the present trial in September 1953. In a week his temperature has dropped to normal and remained so since then. Acid-fast bacilli have disappeared from his sputum by December 1953 and his weight increased from 102 lbs. to 121 lbs. He had no clinical signs of active leprosy left at the beginning of the trial, and was bacteriologically negative.

Case 9. Male, aged 40. Admitted in March 1952 with lepromatous leprosy and open tuberculosis of lungs. Put on thiosemicarbazone. In September 1953, changed to the present trial. Acid-fast bacilli disappeared from sputum by December 1953. Weight increased from 86 lbs. to 109 lbs. From the point of view of leprosy he was still bacteriologically positive at the beginning of the trial, but there were no definite clinical signs of activity left. By June 1954 he became bacteriologically negative, but his clinical appearance has not changed.

Case 10. Male, aged 25. Admitted to a segregation village in 1948 with lepromatous leprosy. Open tuberculosis of lungs diagnosed in April 1952. Transferred to the settlement on thiosemicarbazone, and in September 1953 put on present trial. Acid-fast bacilli disappeared from sputum by November 1953; weight increased from 114 lbs. to 120 lbs. Neither bacteriological no clinical improvement in leprosy during the trial except that the bacilli for the first time showed signs of "granulating" in March 1954.

Case 11. Male, aged 18. Admitted in February 1952 to a segregation village with tuberculoid leprosy. Open tuberculosis of lungs diagnosed in May 1953. Transferred to the settlement and put on thiosemicarbazone, and then in September 1953 on the present trial. Acid-fast bacilli disappeared from the sputum by November 1953, weight increased from 99 lbs. to 116 lbs. There were no signs of active leprosy left at the beginning of the trial, and he was discharged symptom free in May 1954.

Case 12. Female, aged 30. Admitted to a segregation village in

January 1950 with lepromatous leprosy. Open tuberculosis of lungs diagnosed in September 1952. Transferred to the settlement and changed from DDS to thiosemicarbazone. She had been constantly running a high temperature, and developed laryngitis and tuberculous peritonitis with gross ascites. At the time of the beginning of the trial she was nearly moribund. She was put on streptomycin 1 gram daily for a week, with isoniazid, and then changed to 1 gram on alternate days. The improvement was dramatic. Laryngitis has resolved and ascites nearly disappeared. However, acid-fast bacilli continued in the sputum, and she kept on running evening temperatures although not as high as she has had before the present treatment was started. In February 1954 she was changed from streptomycin to PAS without any visible improvement. Her leprosy has not appreciably improved during the trial clinically or bacteriologically.

Case 13. Female, aged 50. Admitted in October 1946 with lepromatous leprosy. On DDS from February 1951. Open tuberculosis of lungs diagnosed in March 1951. In March 1952 put on thiosemicarbazone; in September 1953 on present trial. Acid-fast bacilli disappeared from sputum by November 1953; weight increased from 85 lbs. to 100 lbs. Her leprosy was already bacteriologically negative at the beginning of the trial and there were no signs of active leprosy.

Case 14. Male, aged 30. Admitted to a segregation village in December 1948 with lepromatous leprosy. Put on DDS in 1951. Open tuberculosis of lungs diagnosed in November 1953. Transferred to the settlement and put on the present trial. Evening rise of temperature to 99° subsided in three weeks. As the acid-fast bacilli in sputum had not disappeared, by March 1954 the development of resistance to streptomycin was suspected, and the patient changed to PAS. There were no acid-fast bacilli in sputum by April 1954; Weight increased from 112 lbs. to 139 lbs. From the point of view of leprosy he had clinically only thickening of ears. Bacteriologically he had above ten bacilli per field in his skin smears. There has been no change clinically during the trial, but the bacilli in smears were reduced to below 10 per field.

Case 15. Male, aged 40. Admitted to segregation village with tuberculoid leprosy in 1947. Open tuberculosis of lungs diagnosed in November 1953. Transferred to the settlement and put on the present trial. Evening rise of temperature to 99° subsided in four weeks, and acid-fast bacilli disappeared from sputum by February 1954. Weight increased from 105 lbs. to 126 lbs. The leprosy was already inactive at the beginning of his trial.

Case 16. Female, aged 40. Admitted to a segregation village in August 1952 with tuberculoid leprosy. Put on DDS. Physical signs of tuberculosis of lungs and scanty acid-fast bacilli in sputum found in November 1953. Transferred to the settlement and put on the present trial in February 1954. Acid-fast bacilli did not reappear in sputum, and physical signs subsided. In the beginning of the trial she had large well defined erythematous macules all over her body. There was no improvement after four months of treatment with streptomycin and isoniazid.

Case 17. Female, aged 25. Admitted to a segregation village in October 1952 with lepromatous leprosy and put on DDS. In February 1954 she was transferred to the settlement because of tuberculous lymphadenitis of cervical glands with sinuses discharging pus. She was put on the present trial. Inflammation of glands subsided and sinuses healed promptly. There was no clinical or bacteriological improvement in her leprosy during the four months of treatment.

Case 18. Male, aged 30. Admitted in April 1953 with tuberculoid leprosy. He had a persistent hoarseness which was suspected to be possibly due to tuberculous laryngitis. Therefore he was put on thiosemicarbazone. In January 1954, transferred to the present trial. However, his hoarseness continued, and after five months of treatment without effect it was assumed that his condition was not due to tuberculosis. His case is interesting from the point of view of leprosy. At the beginning of the trial he had scattered vividly erythematous macules with marginal elevation almost resembling a reactional stage of tuberculoid leprosy. There was no improvement whatever following five months of treatment with streptomycin and isoniazid.

CONCLUSIONS.

These have to be considered separately from the point of view of action of the drugs on tuberculosis and on leprosy.

As described before, until the introduction of treatment with thiosemicarbazone the outlook for our patients who had developed severe tuberculosis of lungs was very bleak. The diagnosis of open tuberculosis of lungs was for them almost tantamount to the verdict of death. The situation had improved with the introduction of treatment with thiosemicarbazone. The death rate had fallen to a great extent but only one patient had been cured of the tuberculous infection. Some of the remaining ones improved but all continued to discharge bacilli in their sputum and one (case 12) was actually on the point of death when put on the streptomycin and isoniazid treatment. With the introduction of this treatment, the situation has changed radically. After few weeks, a great subjective improvement was noticed in all patients. They were almost in a state of euphoria, extremely grateful for the " new treatment ". In two to four months, in all except one (case 12) acid-fast bacilli have disappeared from the sputum, although in one of them it did not happen until he has been changed from streptomycin to para-aminosalicylic acid. One patient (case 3), who arrived with acute tuberculous pneumonia at the beginning of the trial, has shown just as good results as the others. The same can be said about one patient (case 17) who was suffering from tuberculous lymphadenitis. None of the patients has had any side effects from the treatment, and in none of them has there been any need to stop treatment even temporarily. Only one patient (case 12) has shown disappointing results although there is little doubt that the treatment has at least for the time being saved her life.

The situation is different where the action on leprosy is concerned. All these patients have been already receiving treatment before the beginning of the present trial, either with DDS or thiosemicarbazone. Only in ten of them leprosy has been still active. Two were tuberculoid and ten lepromatous. No improvement has been observed in the two tuberculoid cases after four and five months of treatment respectively. Among lepromatous cases no bacteriological improvement has been seen in cases 3, 12 and 17. There was slight bacteriological improvement in cases 3, 10 and 14. Cases 5 and 9 had no clinical signs of leprosy left at the beginning of the trial but skin lesions were bacteriologically positive. They became bacteriologically negative during the trial. However, one has to bear in mind that these patients have had a long period of treatment with DDS or thiosemicarbazone, and the reduction in number and disappearance of bacilli might have been the delayed result of

previous treatment. No obvious clinical improvement has been observed in any of the patients.

Conclusions are that the treatment with streptomycin and isoniazid can be highly recommended in tuberculosis complicating leprosy, particularly in leprosaria situated in tropical countries with limited medical staff and no facilities for individualised treatment by specialists in tuberculosis. On the other hand, these experiments seem to show that treatment with isoniazid and streptomycin and also conceivably isoniazid and para-aminosalicylic acid cannot be recommended as treatment for leprosy. They seem to be definitely inferior to sulphones and thiosemicarbazone, apart from being much more expensive. It appears that even in the treatment of tuberculosis in leprous patients, it would be advantagous to combine them with either sulphones or thiosemicarbazone in order to deal effectively with patient's leprotic condition.

SUMMARY.

1. Until the introduction of thiosemicarbazone there has been in the Benin-Delta Leprosy Control Area in Nigeria a very high mortality rate among leprosy patients with tuberculosis even after the introduction of sulphone drugs.

2. Thiosemicarbazone had diminished appreciably the mortality rate but only one patient had been cured of tuberculosis with that drug during 18 months of treatment.

3. In September 1953 all patients with tuberculosis of lungs and lymphatic glands were put on a treatment with 1 gram of streptomycin on alternate days and 100 mg. of isoniazid twice daily.

4. In two to three months the sputum of 14 out of 16 has been rendered free of acid-fast bacilli, and the tuberculosis of cervical glands of the only patient on trial with tuberculosis of lymphatic glands has completely regressed. Two patients whose sputum has not been cleared of the bacilli in 4 to 5 months have been changed from streptomycin to PAS, and the sputum of one of them became free of bacilli in a month. Only one patient went on discharging bacilli after nine months of treatment, but there is no doubt that the treatment has saved her life. The weight of all patients increased considerably, there has been noticeable subjective improvement. There have been no side effects and no need to discontinue treatment.

5. No appreciable improvement in the leprotic condition of the patients has been observed.

6. Treatment with isoniazid and streptomycin or para-aminosalicylic acid is highly recommended for leprosy patients with tuber-

culosis. In view, however, of the doubtful action of these drugs on leprotic condition, it is recommended to combine this treatment with sulphones or thiosemicarbazone.

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THE TREATMENT OF LEPROSY WITH TB1/698.

A REPORT BASED ON 38 MONTHS' EXPERIENCE.

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The use of TB1 698 (para-acetamidobenzaldehyde thiosemicarbazone) in leprosy started here in October 1950 in a small group of cases, and it has been used continuously since then on an increasing scale. It has now (Dec. 1953) been used in 273 cases for periods up to 38 months. A preliminary report (1) covering 12 months' treatment, and an interim report (2) covering 30 months' treatment, have already been published. The present report in general confirms and amplifies the findings made and the views expressed in these previous reports, but modifies them in certain

respects, since the earlier promise of this treatment has not been entirely fulfilled.

MODE OF ADMINISTRATION.

TB1/698 has been given orally twice a day for six days a week. A break of one day a week has been made, for administrative reasons, and because previous experience with other forms or prolonged chemotherapy of leprosy has shown that this break has many advantages and no obvious drawbacks.

The initial dose is usually either 50 or 100 mg. a day according to the weight and physical condition of the patient; in small children it has been 25 mg. a day. After a few days the dose has been increased to 100 or 150 mg. a day, and after another few days to 150, and in some cases later to 200 mg. a day. 200 mg. a day is the maximum we have used. Treatment has been continuous except (a) for short breaks of about 2 weeks once or twice a year for patients leave and (b) when intercurrent disease or complications have made a temporary stoppage of treatment advisable.

TOXIC EFFECTS OF TB1.

Under this head I discuss the bad effects apparently produced directly by the drug itself. The complications arising from the interaction of the drug and the leprous processes are discussed later.

Many reports of the toxic effects of T.B.1 have been published. The early German work on the use of TB1 in tuberculosis was done with doses much higher than those now used, and toxic effects were more common and serious than now. Even with the lower doses at present used, some workers, particularly in the United States, regard the drug as too toxic for the treatment of tuberculosis.

The toxic effects on record include anorexia, headache, epigastric discomfort, vomiting, jaundice and other evidence of disturbed liver function; fever and rashes; a severe anaemia; and agranulocytosis.

In the present series of cases numbering 273, the following complications definitely or possibly due to the direct toxic action of the drug have been seen.

The following definite toxic effects have been seen:—

Acute agranulocytosis	5 cases.
Severe anaemia	6 cases.
Allergic dermatitis	1 case.
Drug fever	1 case.
Acute hepatitis	3 cases.
	16

The following possible toxic effects have been seen:—

Subacute nephritis	2
Psychosis	1
Severe gastro-enteritis	4
	7

DEFINITE TOXIC EFFECTS.

(a) *Acute agranulocytosis.* Five definite and severe cases have been seen, in addition to others showing mild or moderate degree of granulopenia. Four of these serious cases have previously been reported (3). Since then one further case has been seen.

The following are the main features.

All occurred within the first three months of treatment, the number of weeks treatment being 5, 3, 6, 3, 12.

In two cases the patients first complaint was of inflammation of the gums, and of fever with rigors. The other three complained of malaise and fever, and were suspected of malaria; blood examination showed no malaria parasites but revealed the agranulocytosis.

One of the five cases was relatively mild, but four were severe. In the four severe cases, the granulocytes count fell from normal levels before treatment started to very low levels. to 500 or below; the actual lowest counts were 500, 40, 120, and 70, and nearly all granulocytes remaining were eosinophils. In one case, neutrophil polymorphonuclear leucocytes completely disappeared, and in another case they fell to a count of 25.

In one case the agranulocytosis was accompanied by severe hepatitis and jaundice.

In all five cases, TB1 treatment was stopped and one million units of penicillin a day was given until the granulocyte count rose to normal levels, which usually took about seven days; during these seven days the fever (which in some cases was very high, 106) was controlled, but local sepsis developed, in two cases in the mouth, in two in lymph nodes which suppurated, and in one in the nail bed, with necrosis of the end of a toe.

When granulocytes reappeared in the peripheral blood, they were often immature, and sometimes grossly immature.

In three of the five cases of agranulocytosis, after recovery, no attempt was made to resume TB1 treatment; in the other two cases, after a break of about a month, TB1 treatment was cautiously resumed, and has now been continued for many months with no recurrence of the agranulocytosis.

In addition to the five definite cases recorded above, moderate degrees of leucopenia attributable to TB1 treatment have been seen in many other cases, occasionally accompanied by an anaemia apparently due to the same cause, but in none of these has the leucopenia been serious.

(b) *Anaemia.* In several cases during the first few months of TB1 treatment, marked falls in the haemoglobin and red cell content of the blood have been observed. The most marked cases are here summarised.

A young woman before treatment showed haemoglobin 88% (Sahli), red cell count 4.2 millions, and white cell count 6.2 thousands (granulocytes 2000). Treatment was started with 100 mg. a day; three weeks later the dose was increased to 150 mg. a day. After 8 weeks treatment she complained of great and rapidly developing weakness and she was found very anaemic. (R.B.C. 1,050,000; Hb 25%: red cells showed hyperchromia, macrocytosis and poikilocytosis.)

Treatment was stopped and vitamin B 12 was given empirically. A week later the red cell count had risen to nearly 2 millions and the haemoglobin to 44%. A few normoblasts were seen and hyperchromia was marked. Slow but steady improvement was seen, and after three more weeks red cells had risen to 3,200,000 and haemoglobin to 78% (Sahli). TB1 treatment was resumed at a low dosage, 50 mg. a day, but after a few days the low granulocyte count (650) caused a stoppage of treatment. Later, sulphone treatment was instituted with no trouble.

A second case had a tragic ending. After four weeks on TB1 treatment the patient was admitted to hospital for a minor operation under another section, and owing to an oversight was temporarily lost sight of by the Research Unit. After the operation he developed fever and sepsis of a foot, and was treated with penicillin. After a few days the Research Unit traced and examined him and found that the haemoglobin had fallen from 90% to 30% and the red cells from 5 millions to 1.2 millions. The white cells were numerous but grossly immature. The blood picture indicated a severe toxic anaemia and probably a recovering agranulocytosis. Death occurred a day later. This case illustrates the need for continued close observation during the first few weeks of treatment, and perhaps for the avoidance of all surgical operations during this period.

Four similar but less marked cases have been seen. In some of these also, leucopenia has accompanied the anaemia. In some, TB1 treatment was abandoned, but in others, after an interval it has been resumed with caution and continued without serious difficulty,

(c) *Hepatitis.* In many of our patients, during the first few weeks of treatment, a complaint has been made of loss of appetite, "heaviness" in the upper right abdomen, and other symptoms suggestive of mild degrees of hepatitis; in some, laboratory tests have given confirmatory evidence. These symptoms usually subside in a week or two without cessation of treatment.

In three cases, severe hepatitis has developed during TB1 treatment.

In one case it accompanied agranulocytosis as already described, and subsided with recovery. In the second case severe hepatitis and jaundice occurred after six weeks treatment. All the usual laboratory tests for toxic hepatitis gave strongly positive results. The jaundice subsided in a month and a month later TB1 treatment was resumed with no trouble. In the third case, the early months of treatment passed without incident, but in the 7th month a marked enlargement of the liver and spleen was recorded and treatment was stopped for a month and then resumed. During the next few months there were several attacks of malaria. In the 20th month of treatment there was an attack of abdominal discomfort with marked liver enlargement and jaundice, and three weeks later death occurred from subacute liver necrosis.

Comment. These three toxic effects, all of them serious, (a) leucopenia sometimes going on to agranulocytosis, (b) anaemia which may develop rapidly and be very severe, and (c) hepatitis, indicate that the most important toxic effects of TB1 are on the bone marrow and on the liver. During TB1 treatment, especially during the first few weeks, patients should be carefully observed for signs of these complications.

In our experience, clinical observations are more important than laboratory tests. Frequent blood examinations may fail to

detect the impending acute anaemia or agranulocytosis, for these changes may develop quickly after one satisfactory examination and before the next is due. If the patient reports at once if unwell, proper clinical examination will usually detect then promptly, and recovery should occur.

In our series of 13 patients showing these complications, 2 deaths occurred. In one case, the patient ceased to be under our supervision when the complication arose and it was not detected till too late. In the second case, TB1 treatment was continued after one attack of hepatitis, and the second attack was fatal; this case would indicate the inadvisability of continuing TB1 in any patient after an attack of hepatitis.

(d) *Allergic dermatitis.* In our 273 cases treated with TB1, only one severe case of allergic dermatitis has been seen.

After three weeks on TB1, the patient developed malaria which was treated with paludrine. One week later a generalised follicular dermatitis developed, the process involving the mucous membranes and there was a tendency to exfoliation. The condition was very similar to the exfoliative dermatitis due to sulphones, with which we here are very familiar. TB1 treatment was stopped, and antihistamin treatment was given for 3 days, but the dermatitis got worse. Small doses of A.C.T.H. were given for three days with marked improvement, and in two weeks recovery was complete. No attempt was made to resume TB1 treatment, sulphone treatment taking its place. Ten months have now passed with no recurrence of dermatitis.

In a few other cases, a mild follicular dermatitis has been seen on the trunk and arms, but it has not been severe and has soon subsided, in some cases with no stoppage in treatment; in others, TB1 treatment was resumed with no difficulty. In one case, TB1 treatment was abandoned for sulphone.

(e) *"Drug fever".* In one case, the administration of TB1 for the first twelve months was without trouble, and then occurred a continued fever with no apparent cause; when TB1 was stopped the fever stopped and when TB1 was restarted the fever recurred. Finally TB1 treatment was abandoned for sulphone treatment and no further trouble arose. Somewhat similar cases have been recorded by Dharmendra and Chatterji (4).

POSSIBLE TOXIC EFFECTS OF TB1.

Under this head are included three conditions, probably not caused by TB1, but TB1 may have accentuated them. These three conditions are psychosis, subacute nephritis, and acute gastro-enteritis.

Acute psychosis has been seen in only one case, after four months TB1 treatment (carried on with little difficulty although the haemoglobin level was persistently low) the patient became morose, depressed and unmanageable, and this persisted for several months.

Finally the patient was taken home by relatives and has not been seen again.

Subacute nephritis has been seen in two cases. In one there was evidence of mild chronic nephritis before TB1 treatment was started but this became markedly accentuated in the 6th month of treatment. In the second case there was no evidence of nephritis when treatment started, but an attack of subacute nephritis occurred in the 6th month. In both cases recovery occurred, and treatment was resumed.

Acute gastro-enteritis has been the cause of death of three patients during TB1 treatment. This condition is seen in a few of our patients here every year, nearly always in the rainy season. The aetiology is obscure. No organism has been incriminated. It may be seen in patients who are on sulphone treatment, on TB1 treatment, or even on no treatment. It is characterised by high fever, severe abdominal pain, sometimes diarrhoea, sometimes vomiting, (the vomit and the stools sometimes showing altered blood,) by collapse, a falling blood pressure, and in a high proportion of cases, death. At post mortem are seen a large fatty liver, and congestion of and often small haemorrhages into the walls of the stomach and small intestine. In a few cases a plastic peritonitis is seen.

Three fatal cases of gastro-enteritis occurred in our present series of 273 patients, one in the 7th month and one in the 16th month and one in the 18th month. All three cases were in adults, and all showed malaria parasites in the blood at the time of the illness; one had recently had an attack of malaria. It is probable that neither malarial infection nor TB1 treatment contributed much to the fatal termination. In one, the abdominal symptoms suggested an abdominal catastrophe and laparotomy was performed, but nothing definite was found. In all three cases, death occurred within 48 hours of the onset of acute symptoms.

In two of the three cases, post mortem was performed with findings as outlined above.

[In one further case death occurred after a period of TB1 treatment. An old very feeble ill-nourished woman became bedridden and incontinent, and died of cardiac failure.]

RESULTS OF TREATMENT.

(a) *Lepromatous cases with no previous treatment.*

86 such cases are included in our present study. The results may be considered from two points of view, clinical and bacteriological.

The clinical results will be considered first. In almost every case the early clinical results have been good. Slowly but surely the leprous lesions have become less marked, the nodules and infiltrations less obvious, the neuritis less troublesome, the nerves sometimes less thick, eye inflammation less, and so on. Within twelve months in nearly all cases the clinical improvement has been definite or

marked. During the second twelve months, in most cases, improvement has been slower but steady and definite, though there have been some cases in which improvement during the second twelve months has been negligible. During the third twelve months, while there have been some cases in which improvement has continued, there have been others in which improvement appeared to cease, and still others in which definite deterioration has occurred, in a few cases quite rapidly.

To summarise; the early clinical results have been good; the late results have been disappointing in some cases. It seems probable that in some cases with prolonged treatment the drug loses its efficacy, possibly as the result of the bacilli becoming drug resistant.

The *bacteriological results* in these cases are summarised in the following table:—

24-38 months treatment.

Bacteriological status before treatment		*Bacteriological status after treatment*				
		4+	3+	2+	1+	*negative*
4+	10 cases	0	4	4	2	0
3+	7 cases	0	0	2	4	1
2+	8 cases	0	0	2	3	3
1+	5 cases	0	0	0	0	5
	30 cases	0	4	8	9	9

12-24 months treatment.

4+	3 cases	0	2	1	0	0
3+	3 cases	0	1	1	1	0
2+	5 cases	0	0	1	4	0
1+	3 cases	0	0	0	1	2
	14 cases	0	3	3	6	2

6-12 months treatment.

4+	2 cases	0	2	0	0	0
3+	2 cases	0	1	0	1	0
2+	15 cases	0	0	4	11	0
1+	6 cases	0	0	0	4	2
	25 cases	0	3	4	16	2

17 cases with less than 6 months treatment are not analysed.

These results are rather disappointing. While nearly all the cases show improvement, the improvement in some cases is not very marked, even after 3 years treatment. Moreover (though this is

not shown in the table) there are some cases in which earlier improvement has not been maintained, and which are now showing more bacilli than they did a year ago. These results on the whole do not compare favourably with those shown by a similar analysis of similar cases treated with sulphones. The first part of this table may be compared with the following table reproduced from a previous report (5) on results of sulphone treatment for 30-38 months:—

Bacteriological status before treatment		*Bacteriological status after treatment*				
		4+	3+	2+	1+	*negative*
4+	23	nil	2	7	10	4
3+	4	nil	nil	nil	2	2
2+	2	nil	nil	nil	nil	2
1+	6	nil	nil	nil	nil	6
	35	nil	2	7	12	14

Thus, judged from the bacteriological standpoint, the results, particularly the late results, of TB1 treatment are disappointing, and correspond with the rather disappointing clinical results recorded above.

Relapse. 3 lepromatous cases have been classed as "disease arrested" and discharged 15 months, 5 months, and 3 months ago. On re-examination, one of these 3 cases has shown slight relapse, bacteriological but not clinical, a few bacilli only being found on routine examination.

(b) *Lepromatous cases previously treated with sulphone.*

In our present series there were 45 such cases. The reasons for the change from sulphone treatment to TB1 treatment were:—

Severe and repeated "reaction" ...	23 cases
Severe neuritis	10 cases
Eye inflammation	3 cases
Sulphone psychosis	4 cases
Slow progress	5 cases

In the five cases in which progress on sulphone treatment was slow, the change to TB1 treatment produced no apparent increase in the rate of progress.

In the other forty cases in which for varying reasons sulphone treatment was difficult and sometimes impossible, the change was beneficial in practically every case.

In the 4 cases in which psychosis had developed on sulphone treatment, TB1 treatment presented no such difficulty. In the 36 cases in which complications, reaction, neuritis, iritis had made continuous sulphone treatment difficult or impossible, the change was beneficial in practically every case; these complications were not abolished at once but the attacks were rendered less frequent and less severe and finally disappeared, and

moreover the leprosy improved. In some of these patients, however, in the last few months, improvement has become negligible, and in some, sulphone treatment has now been resumed in the hope that recovery will be speeded up.

This group of 45 patients illustrates what is felt to be the most important use of TB1, namely in the treatment of those cases in which sulphone treatment presents real difficulty. In such cases, after TB1 treatment has been given with benefit for 1 or 2 years, after complications have died down and the disease become more quiescent, the resumption of sulphone treatment may be desirable.

(c) *Tuberculoid cases with no previous treatment.*

TB1 treatment has been given to 110 cases of leprosy of the milder tuberculoid type. Almost all of these cases were bacteriologically negative when examined by ordinary methods, so improvement has to be judged on clinical grounds, by the subsidence of activity of the skin lesions as shown by the cessation of spread, by the disappearance of the thickening and erythema, by the diminution of depigmentation and sensory change, by the diminution in thickening and tenderness of nerves, and so on.

Judged on these grounds, the results of treatment have been good. Often within six months, and usually within twelve months, signs of activity have subsided, although depigmentation of the affected areas of skin, and thickening without pain and tenderness of the affected nerves have often persisted. Treatment has lasted for between 18 and 24 months in most cases before discharge. On the whole the results in these cases have been as good as those observed after a similar period of sulphone treatment.

While on the whole the subsidence tended to be slower than with sulphone, it has seemed more often to be accompanied by a return of pigment and sensation to the affected areas of skin. The subsidence of nerve thickening was also perhaps more marked.

Relapse. Of the 110 such cases so far treated, 39 have already completed their treatment and been discharged, the period since discharge now being up to 15 months. Of these 39, 33 have attended for re-examination at least once, and some several times since discharge, and of the remaining 6, 3 are not yet due for re-examination. Of the 33 actually re-examined, 3 have shown signs of re-activation of the disease, all of them at the first three-monthly examination after discharge. In one of these three, the treatment had been inadequate (for twelve of the standard eighteen months treatment, as an experiment, the TB1 had been given twice weekly and not daily) but in the other two, full treatment had been given for 19 and 21 months. All three relapses were slight.

In similar tuberculoid cases, slight relapses have been seen

after a similar period of sulphone treatment; and these relapses also have usually occurred within a few weeks or months after the cessation of treatment; late relapses not having been seen.

These findings of relapse after TB1 treatment are therefore not entirely unexpected, although they do indicate that in this respect TB1 treatment appears no better than sulphone treatment.

(d) *Tuberculoid cases previously treated with sulphones.*

Thirteen such cases have been treated with TB1. The causes of the transfer from one drug to the other are here summarised:—

Sulphone psychosis	2 cases
Severe neuritis	1 case
Slow progress	5 cases
Severe tuberculoid reaction ...	1 case
Relapse after sulphone ...	1 case
Sulphone dermatitis	2 cases
	12 cases

All these cases responded in the usual way to TB1 treatment, but there was no clear indication that the response was any better than continued sulphone treatment would have given (except of course in sulphone psychosis and dermatitis when continued sulphone treatment was impossible).

Thus TB1 treatment of tuberculoid cases has given results which are considered good, about as good as, and in some respects perhaps better than the results of sulphone treatment. Relapses have occurred in some discharged patients, but a comparison of relapse rates is not yet possible for data are insufficient.

(e) *Other cases.*

Nine cases of " border line " type have been treated for periods up to 30 months. The clinical response has been good, and three have become bacteriologically negative. One was discharged after 25 months treatment, and 3 months later showed a bacteriological relapse with numerous bacilli in the nasal discharge. This was unexpected; during several years experience of sulphone treatment we have not made such a finding in discharged patients.

Only 2 cases of " indeterminate " type are included in our present series, and they have been treated for only a short time.

COMBINED TREATMENT WITH SULPHONE AND TB1.

Sulphone treatment, here used in the form of oral administration of diamino-diphenyl sulphone, is of established value and is now the routine treatment of leprosy in most centres. TB1 treatment, though still experimental, appears to have a very definite

value in leprosy. It was therefore thought worth while to study the value of the two drugs given together. We were advised however that a synergistic action of the two drugs was unlikely, in spite of the fact that sulphone, and not TB1, is inactivated by para-amino benzoic acid, which fact would suggest that their modes of action are somewhat different.

Three young men in good physical condition were selected for the first trial. Their leprosy was completely untreated. The dose used was 100 mg. of each drug daily. In one of the three cases in 3½ weeks fever and a generalised dermatitis developed. Treatment was stopped. Later observations showed that he had become intensely allergic to sulphone. In the other two cases the combined treatment continued for longer but the patients complained of headaches and malaise and there was no obvious advantage of the combination of the two drugs over either drug given alone. The trial was stopped.

Later a further attempt was made to study combined treatment. 9 patients were selected who had been receiving one or other treatment for widely varying periods and who were showing a poor response to that treatment. In the first case, previously on TB1 treatment 150 mg. a day, the dose used for combined treatment was 100 mg. of each drug daily. Within four weeks he developed fever and allergic dermatitis, and a few days later an acute psychosis. Treatment was stopped and the toxic manifestation subsided. Later, sulphone treatment alone was used with no trouble.

Thus of 4 cases in which sulphone had not previously been used, when it was given in combination with TB1, serious toxic effects were seen in 2. The TB1 appeared to enhance the toxicity of the sulphone.

In the remaining eight cases, the previous treatment had been with sulphone and had been well tolerated, but response had been unusually slow or inadequate. The dosage used was in most cases 150 mg. of TB1 daily and 400 m.g. of DADPS twice weekly; in two cases daily DADPS was used instead of twice weekly, the dose being 100 m.g. in one and 200 m.g. in the other.

In one of the eight cases, severe anaemia caused the abandonment of the combined treatment in 2 months. In two others, severe reaction at the 3rd and 4th month caused its cessation. In the five others, though complaints of headache and malaise were not uncommon, the combined treatment caused no serious trouble and was continued for 6, 6, 15, 22, and 28 months in the five different cases. No obvious benefit was seen from the combined treatment, progress appearing no quicker than with either drug given alone.

Combined treatment was therefore abandoned.

TB1 IN PREGNANCY, THE PUERPERIUM, AND LACTATION.

Previous experience with sulphone has shown its value in maintaining the health of the mother during pregnancy and in preventing the aggravation of leprosy so often seen in untreated cases during the puerperium. It has been found possible to continue sulphone treatment during the whole of pregnancy, the puerperium and lactation. Further, sulphone is excreted in the mothers milk and may be of value in combating possible leprous infection of the baby. (In East Nigeria as in many parts of Africa, there is no real alternative to breast feeding because there are no cows). Moreover serious toxic effects in the baby have not been seen.

The question arises whether the same is true of TB1. The

toxic effects of TB1 are such that if they occurred during pregnancy they would be very serious. It may be unwise to start TB1 treatment during pregnancy and we have not done it. Some women already on TB1 treatment have become pregnant, and have continued the treatment with benefit through pregnancy the puerperium and lactation, with no untoward results to themselves* or in most cases to the child. In one case however, a child has shown signs and symptoms which appeared to be those of the toxic effects of TB1, a marked anaemia of toxic type which recovered promptly when the mother's TB1 was stopped. It was perhaps significant that in this case the TB1 treatment was started when the child was a few months old.

Chatterji and Bose (6) have shown that if a mother receives TB1, her milk contains TB1 but in such small amounts that toxic effects to a baby would appear unlikely. Nevertheless on general grounds, and on our limited experience of TB1, we regard sulphone treatment as preferable during and after pregnancy.

TUBERCULOSIS DEVELOPING DURING TB1 TREATMENT OF LEPROSY.

Both the drugs used in the treatment of leprosy, sulphones now being used as the routine treatment, and TB1 now being used experimentally, were originally introduced into medicine for the treatment of tuberculosis, although they are not now widely used for this purpose.

A study of the incidence and severity of tuberculosis in those receiving these drugs for leprosy may be of interest.

Reports from the National Leprosarium Carville Louisiana U.S.A. (7) state that since the introduction of sulphone as the routine treatment for leprosy, the incidence, severity and mortality of tuberculosis of the lungs in leprosy patients has markedly diminished. Experience here at Uzuakoli Nigeria has been similar, and it should be emphasized that in our Africans, tuberculosis often arises acutely and develops rapidly. In several hundreds of cases of leprosy I have observed, no case of tuberculosis arising after sulphone treatment has been well established and maintained for several months. Two or three cases have been detected during the first few weeks or months of sulphone treatment, and it appeared likely that the disease had originated before sulphone treatment was introduced. Moreover the severity of the disease seems to be modified by the sulphone treatment. There is evidence that sulphone is exerting a suppressive action on tuberculous infection,

*Since this paper was drafted, one case has been seen of exacerbation of leprosy during the puerperium in a woman receiving TB1 treatment.

and in combination with streptomycin and isoniazid we have used it with apparently some effect in treatment. Is the same true of TBI?

Here again our experience is limited. In our 273 patients treated up to 38 months with TBI, two new cases of tuberculosis have arisen, one in a patient after 9 months treatment and the other in the 6th month of treatment. There was no evidence that the disease had been present before TBI treatment started. In neither case was the disease severe.

So far our experience suggests that the suppressive action of TBI on tuberculosis is less marked than that of sulphone.

DISCUSSION AND CONCLUSIONS.

An attempt has been made to present the relevant facts of our experience of TBI in the treatment of leprosy during the last 38 months, with a view to assessing the part it should play in the treatment of leprosy.

There is no doubt that TBI has a beneficial action in most active cases of leprosy, but many questions arise regarding toxicity and efficacy, and the simplest and most useful way of discussing these questions is to make a comparison between TBI treatment and sulphone treatment of similar cases.

Compared with sulphone treatment TBI has two advantages:

(1) In patients who have difficulty with sulphone treatment because of the severe and repeated attacks of reaction erythema nodosum, neuritis, iritis, etc. which it may provoke, TBI is almost always better tolerated, and is beneficial.

(2) In some patients, clinical improvement under TBI treatment appears for a time at any rate more marked than in similar patients on sulphone treatment.

On the other hand TBI treatment has several disadvantages compared with sulphone.

(1) While toxic effects of the two drugs are seen in about the same proportion of cases, TBI is more dangerous, since it has a toxic effect on bone marrow and on the liver. It should not be used except under close medical supervision.

(2) While the early results, judged clinically and bacteriologically, of TBI treatment appear to equal those of sulphone treatment, the late results of TBI treatment appear less satisfactory. A considerable proportion of patients after 2 years or more TBI treatment with good progress, reach a stage where the drug seems to lose its action, and further progress is not seen; moreover in several

such patients, definite clinical and bacteriological deterioration has set in; in our experience with sulphone treatment this has not occurred. We are gradually being forced to the view that in the long run TB1 treatment is less effective than sulphone treatment.

(3) Sulphone treatment while it can be given daily, can also be given twice weekly, once weekly, or according to some workers, once fortnightly. In our experience, TB1 treatment has to be given daily and preferably twice daily to be effective. This renders the treatment much less widely practicable.

(4) The cost of TB1 treatment is several times as great as oral treatment with diamino-diphenyl sulphone. With several thousands of patients to be treated, this difference may be important.

For these reasons it is considered that TB1 treatment of leprosy should be confined (a) to patients who become allergic to sulphones (b) to patients who suffer serious toxic effects of sulphone e.g. psychosis and (c) to those patients in whom for any other reason sulphone administration present difficulties e.g. severe or repeated reaction neuritis, eye inflammation etc. In this third group of cases, when the patient improves sufficiently on TB1 treatment, sulphone treatment should be resumed if possible.

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REVIEWS.

Lepra. Gomez Orbaneja, Jose and Garcia Perez, Antonio. 387 pp., 105 figs. (1 coloured on pl.) 1953 Madrid: Editorial Paz Moutalvo [45s.].

The book is divided into 11 chapters. The first two describe the aetiology and general pathology of leprosy infection. Chapters 3 to 7 give a description of the classification, and details of the 4 forms of the disease: indeterminate, tuberculoid, lepromatous and borderline. Chapter 8, with 63 pages, discusses the diagnosis fully from every point of view. The last 3 chapters are devoted to treatment, epidemiology and prophylaxis. There are 4 appendices dealing chiefly with rules and regulations for the control of leprosy in Spain. A bibliography is added.

In the preface the authors set forth the objects of the book. Much has been learned recently of the clinical aspects and the relationships of the various forms, there is new light on the question of resistance, and new and more effective forms of treatment have made it more possible to control the disease and efface its effects. They feel that when so much progress is being made and so much interest taken in leprosy, both in Spain and in other Spanish-speaking countries, there is need for a book which will give the latest information on the subject. The authors may be congratulated on their success in carrying out the objects which they set themselves. The arrangement of the subject matter in chapters and sections of chapters, the logical way in which arguments are set forth, the clarity of the style and the appropriateness and clearness of the illustrations, make easy and pleasurable reading. Recent world-wide literature has been read and digested by men with personal practical knowledge and experience, and they have thus been able to put together within a convenient compass a remarkable degree of detail.

The method of arrangement may perhaps be best illustrated by reference to chapter 2, which deals with the general infection of leprosy. The penetration of the organism by the bacillus is first described. Next are considered the possible responses of the organism to the penetrating bacillus and the factors which influence these responses, and which may belong either to the organism or the bacillus. Age, sex, race, heredity, constitution, climate, food, intercurrent diseases and the standard of living are next fully discussed. This is followed by a section in which the various aspects of immunity are set forth. The chapter continues with a description of the pathogenesis of the various syndromes of leprosy, those of the

skin, nerves, internal viscera, eyes, nose and throat, endocrines and lepra reacation. Lastly there is a section on the biochemistry of leprosy infection.

The book is well printed and bound, and of a convenient size. It should be of great value in Spain where a determined and well-planned campaign is rapidly bringing the disease under control, and also in Latin America and other Spanish-speaking parts of the world where leprosy is still endemic. ERNEST MUIR.

" Leprosy " by James A. Doull. Veterans Administration Technical Bulletin.

This bulletin of seventeen pages has been written by the Medical Director of the Leonard Wood Memorial (American Leprosy Foundation), presumably with the object of guiding the Veterans Administration in dealing with the matter. Perhaps it is unnecessary to state that " veterans " in the United States are ex-servicemen in Britain. To deal with leprosy in such a short pamphlet is no easy task, and it might be thought that such an account of leprosy is bound to be superficial and of little interest to those who have long studied the subject. Reading the pamphlet will show that this is not true. The reviewer has read it with great interest and finds it one of the most interesting presentations of this subject which he has read.

The following is a brief summary:—

After defining leprosy and its main types, the author gives an interesting discussion of the history of the disease. The reviewer found the following paragraph of interest:—

" The principal source of leprosy on the American continent is supposed to have been infected slaves from Africa, although there is little doubt that French, Portuguese, and Spanish immigrants also carried the disease. In Mexico, there is a story that the severe Lucio variety, which is described later, is of Chinese origin. Leprosy was brought to the Upper Mississippi Valley by Scandinavian immigrants early in the 1800's. Data given in a recent study by Washburn (6) indicate that there were about 170 Scandinavian immigrants who developed leprosy, of whom 52 had the disease before leaving Norway. At least 76 were reported from Minnesota and most of the others from Wisconsin, Iowa, the Dakotas, and Illinois. In Minnesota, 7 cases occurred in American-born persons of Scandinavian parentage but only one in the third generation. There is no record of subsequent cases in other States. In Louisiana, the disease is thought to be of French origin and this is true also of a small focus at Tracadie, in New Brunswick, Canada."

The geographical, sex and age distribution are discussed. It is considered that leprosy is commonly contracted in childhood but that, as the disease declines, the average age of onset may increase. It is stressed that it is not uncommon to contract the disease in adult life, and that prolonged residence in an endemic area, or prolonged contact, is often not necessary.

The account of the incidence of leprosy in American ex-servicemen is of some interest. After the Spanish-American War, 32 cases were recorded in service personnel; after World War 1, 51; of these 33 had not had war service outside the United States but 18 had been born outside and many came from the Southern States, where leprosy is endemic; not one came from the Northern States, where there is practically no leprosy. It is obvious that military service did not explain most of the cases. The same remarks apply to the cases, numbering 77, which Dr. Doull has traced following World War II. Most of these had possible or probable sources of infection apart from their military service. Dr. Doull mentions the two soldiers who developed leprosy after being tatooed at the same time by the same tatooer in Melbourne, Australia, the first lesion appearing at the same time in the tattooed area in both cases.

Under aetiology are discussed the bacillus, attempts at transmission to man and other animals, attempts at culture, and so on. The writer regards the lepromatous type as constituting the principal, if not the sole, source of infection. Accidental transmission is discussed and a well-known case recorded by Marchoux is cited. There is a section on leprosy-like diseases in animals. There is a short but reasonably good account of pathology, of the lepromin reaction, and of classification. The clinical description of leprosy is short but fairly comprehensive. The account of diagnosis is useful. The section on treatment includes a useful summary on the findings of the therapeutic trials conducted by the Leonard Wood Memorial. The following two sentences record Carville experience of the late results of treatment:—

"He (Erickson) studied the probability of arrest, defined as a 1-year period of negativity of skin and mucous membranes from M. leprae and freedom from clinical evidence of activity, and found that it increased from 3.6 percent by the end of the second year of treatment to a total of 73.0 percent by the end of the ninth year. Relapse occurred in 6 of 33 patients who were followed from 1 to 5 years after apparent arrest."

In the section upon control, the following paragraphs appear worth quoting:—

"There is no method for the prevention of leprosy which has been demonstrated to be effective. Granted that present-day theories regarding sources of infection and modes of transmission are correct, the practice of separating lepromatous patients from healthy contacts is a logical procedure. In practice it is of very limited application because of the expense which is involved. Countries in which the disease is frequent and which have attempted to provide sanatorium care for all lepromatous patients, as for example the Philippines, have found the burden extremely heavy. The effectiveness of the procedure is related to the duration of the infectious stage prior to discovery of the disease. In the Philippines, the attack rate for household associates remained high during a long period in which compulsory segregation of bacteriologically positive patients was in force.

"Leprosy is a disease in which the balance between the host and the parasite is nearly equal. The disease has persisted for long periods in most

areas where it is prevalent, yet it seldom exhibits any tendency to increase markedly. In the individual, it exhibits a very chronic course with a tendency towards recovery. It would seem, therefore, that wide and properly directed use of the sulfones might, by healing lepromatous ulcers and shortening the period of infectiousness, have a favorable effect not only on the individual patient but also on the trend of the disease. Outpatient centers should be established in every area where the disease is endemic and efforts be made to treat all lepromatous patients. In the past 5 years much has been done in this direction in the Belgian Congo and certain other countries. At the same time, therapeutic research is necessarily directed especially towards discovery of a drug with bactericidal properties."

The final paragraph on BCG stresses the need for more experiment before definite opinions on its value can be expressed.

NEWS.

FRANCE.

In the 1954 session of the National Assembly of France a resolution was tabled and, we are informed, passed, proposing the laying down through the United Nations Organisation of an international statute for leprosy patients, establishing their rights as human beings. A copy of this resolution which has reached us is accompanied by a copy of the speech supporting it, which states how a Frenchman, M. Raoul Follereau, has studied the matter for ten years in all parts of the world and is appalled by the denial of human rights to those with leprosy which he has found. The United Nations Charter, Article 13, proclaiming to all the enjoyment of the rights and fundamental liberties of man, and the Dumbarton Oaks statement to the same effect, are quoted, and the exclusion of those with leprosy from these rights is denounced. The speech states that leprosy is a disease like any other, and much less serious and much less contagious than some, tuberculosis for example; that the disease is now held in check by treatment, and that within 50 years it may be completely conquered; that there are at least ten or twelve million persons with leprosy in the world living under physical and social handicaps of great severity, often quite unnecessarily. The speech proposes that a declaration of the United Nations should solemnly proclaim that the maintenance of leprosy prisons is unworthy of nations claiming to be civilised, that the United Nations Organisation should recommend the closure of such leprosy institutions and their transformation into sanatoria for the proper treatment, care, and ultimate discharge of the patients, with return to their employment and social life with no discrimina-

tion, and that the Assembly of the United Nations Organisation shall recommend to all member countries that a census of patients with leprosy shall be made by a specially appointed staff, and shall solemnly proclaim that these patients are under the common law and protected by it, and that they shall be guaranteed their liberty as soon as responsible doctors declare them not infectious, and that they shall be given the same facilities, advantages and privileges as all other citizens, without exception.

NYASALAND.

The following is a quotation from the Annual Report of the Medical Department of the Nyasaland Protectorate for the year 1952:

" At Kocira, the site for the proposed Central Government Leprosarium, work proceeded on little more than a care and maintenance basis, again owing to the restriction of the capital programme. However, much preliminary work was done under the direction of the BELRA Supervisor. Clearing of the estate, brick and tile making, and the establishment of a herd of cattle preparatory to the develoment of mixed farming, went ahead as far as the limited funds permitted.

" The issue of sulphones to Government subsidized Mission Leprosy Institutions continued, and adequate supplies were issued for the treatment of all in-patients and a limited number of out-patients. The visit of Dr. R. G. Cochrane, Medical Secretary of BELRA, already referred to, was an encouragement both to the Missions visited and to the Government staff concerned with the expansion of leprosy control measures.

" The creation of the Brown Memorial Fund during the year was an item of considerable importance to leprosy control in Nyasaland. The late Mrs. M. H. D. Brown and Miss M. A. Brown, formerly tea planters in the Mlanje District, bequeathed their residuary estate ' for the benefit of the lepers of Nyasaland '. After protracted legal proceedings over the validity of the will, the High Court ruled that the Brown Memorial Fund should be established, vested in a Board of Trustees consisting of eight persons of whom three are to be *ex-officio*, namely the Director of Medical Services, the Accountant-General and the Administrator General; five other representative trustees were to be appointed, one by the Governor in Council, one by the Christian Council of Nyasaland, one by the Bishops of the Roman Catholic Church in Nyasaland, one by the African Protectorate Council and one by the Nyasaland Branch of the British Red Cross Society.

"The objects of the Fund, which totals some £232,000, are to make grants and periodical payments, as the Trustees think fit, towards the development and upkeep of institutions providing treatment for Nyasaland lepers; provision is also made for the support of leprosy research work in Nyasaland.

"A preliminary meeting of the Trustees was held on the 10th December, 1952, and the fully constituted Board of Trustees is to start work early in 1953."

REPORTS

Bulletin Médical de L'Afrique Occidentale Francaise Janvier, 1954.
Tasks and Problems of Public Health in French West Africa.

This special number includes a section of four pages dealing with leprosy work, of which the following is an abbreviated translation:—

The creation of a Central Leprosy Service dates back to November, 1931, when the new Service was formed and placed under the direction of a special physician, with headquarters at Bamako in an institution built for the purpose. The development of anti-leprosy work in French West Africa as a whole, however, was for many years handicapped by administrative difficulties, and the Service remained a research centre, with limited activities outside. In 1945 the arrangement was revised and the activities of the Leprosy Service were incorporated into the Service d'Hygiène Mobile and its activities greatly extended.

The anti-leprosy campaign in French West Africa relies principally upon the detection of leprosy cases and their treatment. Segregation has been abandoned as ineffective and legally indefensible. Cases of leprosy are admitted to leprosaria but they are being transformed slowly to true health institutes, and the patients, although still maintained under certain discipline, can leave the leprosaria whenever they wish. This liberty permitted to those with leprosy with obvious lesions, has aroused in the larger towns a reaction of European opinion, which still believes in the isolation for life of those suffering from leprosy. In fact, the isolation of those with leprosy can only be applied to those with active infectious leprosy, as laid down by law; it can also be justified for those who have become so disabled that they cannot support themselves.

All the leprosaria carry on two main functions:—(1) the function of a hospital for the treatment and isolation of active infectious cases, and (2) the function of an asylum for patients who have become disabled. Whilst most of the leprosaria of the Federation are forced to refuse patients admission because of lack of room, in certain large towns, such as Dakar, there is difficulty in getting the patients into the institutions, partly because they can maintain themselves by begging. Here again, ill-informed public opinion has expressed itself.

The detection of cases. This is carried out by survey units. In certain areas the whole population is examined every year, in other areas less frequently. In December, 1952, the number of cases of leprosy recorded as living in French West Africa was 135,000, but the Mobile Health Service does not cover the whole territory, and the total is estimated at 250,000 in a population of 8 million. By contrast, in L.A.M., with 9 million population, the number of leprosy cases recorded was only 23,000. This difference is attributed partly to the Mobile Service method of work in French West Africa, whereas in L.A.M. the patients detected are only those who report themselves spontaneously.

Treatment. In 1952 there were 36 leprosaria, with 1,700 patients. The vast bulk of the patients are dealt with in sub-centres, which in 1952 numbered 400, where the patients attend once a week. Between 1946 and 1949 chaulmoogra oil was the main medicament used. Since 1949, sulphone treatment has been used on a small but increasing scale, and recently the introduction of treatment by injections of D.D.S. in oil, allowing treatment at long intervals, has made it possible to extend the use of sulphone treatment. In 1952, of the 60,000 patients under treatment, 10,000 received sulphone and 50,000 received chaulmoogra oil. In 1953 the use of sulphone was greatly extended, and 1954 should see sulphone treatment extended to 40,000 patients.

Leprosy in Netherlands New Guinea. South Pacific Commission. Technical Paper. No. 56.

Leprosy in the Trust Territory of the Pacific Islands. South Pacific Commission. Technical Paper. No. 57.

These two reports were prepared for the South Pacific Commission by Dr. Norman Sloan, who was appointed Leprologist to the Commission to study and advise with regard to leprosy problems in their area. Dr. Sloan spent 6 months (May-Oct. 1952) in the

Netherlands New Guinea and 3 months (Dec., 1952-March, 1953) touring the Trust Territory of the Pacific Islands. Conditions in these two areas were quite different, but it is interesting comparing the leprosy problems found in each.

Dutch New Guinea is a large land mass with a few outlying islands with an area of 150,000 square miles (3 times the size of England), whereas the Pacific Islands have a land area of 687 sq. miles spread over 3 million sq. miles. The population of Dutch New Guinea is about one million (6 per sq. mile) whereas that of the islands is 55,000 (80 per sq. mile). In the administered areas of Dutch New Guinea the people who live on the coast or the islands dwell closely crowded together in insanitary conditions, which tend to the spread of infectious diseases. The vast interior was not visited owing to the difficulty in transport. Malaria, tuberculosis, yaws, filariasis and worms are very prevalent, and infant mortality is appallingly high in the first two years of life, being 40-50%. The staple diet is sago. In the Pacific Islands, on the other hand, the islands are small, scattered and relatively healthy. Malaria, yaws and filariasis are uncommon, though tuberculosis is on the increase. Infant mortality is not mentioned and is probably not a problem. Diet is varied and adequate.

Owing to the difficulty in transport, only a few places where leprosy was known to be prevalent were visited in Dutch New Guinea, so that only 16,882 persons were examined in 6 months, and amongst these 525 cases of leprosy were found. Probably a large number of cases were not seen.

In the Pacific Islands the small population of each island makes it probable that most of the leprosy cases are known. This makes any comparison between the two regions difficult.

In Dutch New Guinea, of the 525 cases, 300 were benign (i.e. tuberculoid or indeterminate) and 225 lepromatous. Males 285. Females 240. Children under 15 years, 138 (one-quarter of the total).

In the Pacific Islands. of the 223 cases, 175 were benign and 48 lepromatous. Males 137. Females 86. Children under 15 years 20 (one-tenth of total).

In Dutch New Guinea the leprosy problem is serious, and in some areas reaches alarming proportions, e.g. in the Wandammen area on the north coast 221 cases were found amongst 3,296 people examined. A prompt and adequate control programme is therefore recommended with the appointment of a full-time leprosy officer, central leprosarium and four leprosy villages.

In the Pacific Islands the small number of lepromatous cases, and of infected children is very encouraging. Leprosy in the Trust

Area is relatively mild, and the people value treatment and are anxious to receive it, so that there are probably only very few unknown cases. G. O. TEICHMAN.

East African Interterritorial Leprologist. Annual Report, 1953.

In this report the promising developments of antileprosy work in the territories of Uganda, Kenya and Tanganyika are outlined, including the work of Dr. J. A. K. Brown in carrying out surveys and setting up rural control work in Uganda, and the growth of local government leprosaria in various regions of East Africa.

The project of the East African Leprosy Research Centre is outlined, and the early phases of its development are described. In this project the British Empire Leprosy Relief Associaion, the East African High Commission and the Colonial Medical Research Committee are co-operating. The centre is to be developed at the new and growing leprosarium at Itesio, in Kenya, and the building programme is now in progress. The development of work in Uganda is described as follows:—

> "What has been achieved in Uganda is a system of surveys and control based on the people themselves. Leprosaria are not considered outmoded, but are preserved and supported, but a strong supplementary emphasis has been put on rural control of the disease. In propaganda amongst the people, emphasis is placed on county and parish housing of detected cases of leprosy. The tribal authorities are asked to build the re-housing units of detected cases away from other houses, and county or parish treatment centres are built. 'We have the medicine; you get the people organised to receive it.' This is one of the slogans of the campaign, of which the aim is to group the patients reasonably near their homes and near dispensaries, so there is segregation for most of the time and treatment can be given regularly. Dr. Kinnear Brown finds the response of the people good, and considerable progress in the scheme has been made in 1953."

The report contains an account of the International Leprosy Congress in Madrid.

The transfer of Dr. Wheate from the work at Kumi, in Uganda, to undertake work in Tanganyika is recorded. He is now in charge at Makete leprosarium.

A donation of £2,000 from the Mission to Lepers to Makete leprosarium is gratefully acknowledged.

The value of the visit of Dr. R. G. Cochrane, Medical Secretary of the British Empire Leprosy Relief Association, to East Africa is emphasised, and the East African number of the *Leprosy Review* which he published.

The building up of the leprosarium at Itesio is described, and the valuable work of various missions and individuals in leprosy work in Tanganyika is mentioned.

ABSTRACTS

DE ALMEIDA, J. O., DE FREITAS, J. L. P., BRANDAO, H.

"Electrophoretic Studies on the Protein Distribution in the Serum of Leprosy Patient", The Reports of the Research Inst. for Tuberculosis and Leprosy, Vol. 56, No. 3, Jan., 1954. (Japan.)

A quantitative complement fixation test using a triple antigen, made up of cardiolipin No. 72 for syphilis, T. cruzi extract for Chagas' disease, and a tubercle bacillus extract for tuberculosis and leprosy, is presented. Experimental work has been done to establish the basic principles governing the reaction by demonstrating that the specific systems react independently of the presence of other antigens.

Sera from 786 blood donors were tested against the triple antigen and against each one of the specific antigens, in complement fixation tests. The 599 sera that did not react with the triple antigen did not show any reactivity with the antigens for syphilis, tuberculosis, leprosy or Chagas' disease; no false negatives occurred with the triple antigen. The 103 sera which reacted with any one of the specific antigens, reacted also with the triple antigen. Four sera were anti-complementary, simulating "reaction" with the triple antigen; 76 sera gave "reaction" with the triple antigen but did not show any specific reaction in the tests for syphilis, Chagas' disease, tuberculosis or leprosy. These results could be due to the cumulative anticomplementary effect of these sera plus that of the antigens composing the triple antigen.

The preceding results indicate that a screen test employing the triple antigen should be used instead of the regular test for syphilis, in areas where syphilis, tuberculosis, leprosy, and Chagas' disease are endemic. *(Authors' Summary)*

MAYAMA, A.

1953, "Electrophoretic Studies on the Protein Distribution in the Serum of Leprosy Patient", The Reports of the Research Inst. for Tuberculosis and Leprosy, Vol. 56, No. 3, Jan., 1954.

(1) Electrophoretic studies on serum protein were performed in 63 leprosy patients.

(2) Almost no differences were demonstrated in electrophoretic findings between the healthy persons and neuro-macular patients except for far advanced cases.

(3) In lepromatous patients, elevation of total serum protein, a decrease in albumin and an increase in gamma-globulin were demonstrated. Consequently, albumin-globulin ratio were less than 1.0. But any relationship could not be found between electrophoretic findings and clinical conditions.

(4) In lepromatous cases with complication of " erythema nodosum leprosum ", however, more characteristic findings were obtained, viz., remarkable decrease in albumin and significant elevation in gamma-globulin with a rise in total serum proteins.
(5) No parallelism between gamma-globulin component and tuberculostatic activity of the blood was confirmed so far in leprosy patients. *(Author's Summary).*

" INTERNATIONAL MEDICAL ABSTRACTS AND REVIEWS "—Vol. 15, No. 5, May, 1954, is a special leprosy number dealing particularly with the social aspects of leprosy. A symposium on social aspects of leprosy prevention was apparently held recently in Calcutta and the papers published in this issue were contributed to that symposium.

The papers were by: Dr. M. Bose, Mr. S. Roy, Dr. G. Panga, Mr. M. Diwan, Dr. D. N. Bose, Dr. P. Sen.

" LEPROSY IN INDIA." Vol. XXVI, No. 2, April, 1954.

This issue contains editorial notes surveying the activities of the World Health Organisation in relation to leprosy. An article by Dharmendra and K. R. Chatterji reports the study of isoniazid in the treatment of leprosy in 31 patients. The report covers absorption, excretion and dosage. The experiment continued for periods up to 57 weeks. No toxic effects were observed. Early therapeutic results were favourable but the later results were less favourable. The conclusions reached are as follows:—

> " It may be concluded that INH has been found of definite value in the first 8 to 12 weeks, specially in reducing the bacteriological concentration, but that on the whole it is not very effective in the treatment of leprosy, since there is usually a set back in the initial improvement. Neither has it been found of value in the treatment of acute or subacute lepra reaction. It is possible that in combination with some other anti-leprotic drugs, INH may be of some value in the treatment of leprosy. If our assumption regarding the development of resistant strains of leprosy bacilli to INH early in the course of treatment be correct, it would indicate the need for combining INH with some other anti-leprotic drugs (sulphones or thiosemicarbazones) either from the start, or for changing over from INH to one of these drugs after about 2 months of treatment with INH during which initial improvement will be noted in most cases."

Two articles deal with a new sulphone (2:2' Dihydroxy 4:4' Diaminodiphenylsulphone). Dr. Biswas writes a note on preparation and Drs. Dharmendra, Chatterjee and Bose a note on preliminary tests against acid-fast bacilli in vitro. A small test on human beings is planned.

This issue also contains the first report on the World Health Organisation Expert Committee on leprosy and also a report by Mr. W. Bailey of the International Leprosy Conference of the Mission to Lepers and American Leprosy Missions.

DUARTE, I. G. & DE MELLO, P. H.

" Dapsone in the Treatment of Lepromatous Leprosy ", Rev. Brasileira Leprologia. S. Paulo. 1153, Sept., Vol. 21, No. 3, 207-20. (40 refs.)

First the literature of sulphones is reviewed. Then an account is given of 90 cases of leprosy treated with dapsone (DDS). The daily dose given orally was 100 to 200 mgm., the latter being tolerated when 42 days of treatment was followed by 15 days' rest. Having formerly used promin, diasone and other DDS derivatives, the author considers that because of its efficiency, ease of administration and moderate price, DDS is the treatment of choice for leprosy.

ERNEST MUIR.

LAVIRON, P., LAURET, L. & JARDIN, C.

" Contribution to the Study of Delayed-Action Chemotherapy in the Anti-leprosy Campaign in French West Africa. Bull. Soc. Path. Exot. 1954, Vol. 47, No. 1, 127-39, 6 figs. and 6 graphs.

Because of the long distances that have to be covered in Africa a twice-monthly injection of DDS is given. Two suspension media have been used, groundnut oil and chaulmoogra ethyl esters. The latter is preferred as the curve of blood concentration remains more level during the time between the injections. The rate of absorption can also be regulated by the size of crystals used in the suspension. The dose of 1.25 gm. twice a month appears to be sufficient and is not toxic for the African. Details are given of 10 patients treated and an addendum sets out the technique used for estimation of DDS in the blood and in the urine. ERNEST MUIR.

FLOCH, H. & GELARD, A.

" The Use of Delayed-Action DDS in Relation to the Size of Crystals in the Suspension ". Bull. Soc. Path. Exot. 1954, Vol. 47, No. 1, 35-40.

The authors aim at giving patients 1.5 gm. every 3 weeks in suspension in 0.2 per cent. agar saline. They find that the larger the DDS crystals in the suspension the more slowly is the drug absorbed. The dosage given amounts to 0.5 gm. intramuscularly per week; the amount recommended at the Madrid Congress was between 0.3 and 1.2 gm. per week. The authors give 50 mgm. a week for the first month, 1.0 gm. per fortnight for the second 2 months, and then 1.5 gm. every 3 weeks. They find that on the day after the injection there is a blood concentration of 0.460 mgm. per 100 cc. which gradually diminishes but is 0.100 mgm. per 100 c.c. on the 21st day. The rate of absorption can be regulated by increasing or diminishing the size of the crystals in the suspension.

ERNEST MUIR.

LIPPELT, A.

" BCG and Erythema Nodosum in Leprosy ". Rev. Brasileira Leprologia. S. Paulo. 1953, Sept., Vol. 21, No. 3, 221-4.

Two hundred adult lepromatous patients who had been on

sulphone treatment and had improved to a greater or less degree were given 3 gm. of BCG in weekly doses of 200 mgm. by mouth. Some improved and were able to go back to work, but in many there were exacerbations and attacks of erythema nodosum. On the whole the results were not very encouraging. ERNEST MUIR.

JOPLING, W. H. & RIDLEY, D. S.

" Isoniazid in Lepromatous Leprosy. Trans. Roy. Soc. Trop. Med. & Hyg. 1954, Mar., Vol. 48, No. 2, 138-8 (10 refs.).

Eight lepromatous patients were treated for a period of 6 months with isoniazid. Some of them had already been treated with sulphones with poor results. Clinical notes of the 8 patients and laboratory findings are given. The usual daily dose was 1 to 2 mgm./kgm. increasing gradually to 5 mgm./kgm., but there was variation in the amounts tolerated. In all cases there was a certain amount of lepra reaction, so severe in 2 cases that treatment had to be temporarily suspended. There was no evidence of clinical improvement in any of the patients, and though there seemed to be bacteriological improvement in some, it was not maintained. The conclusion confirms the view of Lowe and others that under the conditions of trial isoniazid is not an effective treatment for lepromatous leprosy. ERNEST MUIR.

SHARP, L. E. S.

" A Trial of Iso-Nicotinic Acid Hydrazide in Leprosy ". East African Med. J. 1954, Feb., Vol. 31, No. 2, 59-62.

During 5 months 18 lepromatous and 5 tuberculoid cases of leprosy were treated with isoniazid, 200 mgm. being given daily. The results were that 87 per cent. were much improved or improved, and 13 per cent. were stationary. This computation is based on clinical results, and no mention of bacteriological examination is made. At the same time, and acting as controls, the following number of cases were treated with other drugs, the percentage improvement being shown in brackets: 121 with DDS (84), 128 with DDS and intradermal chaulmoogra oil (95), 27 with thiosemicarbazone (89), 45 with thiosemicarbazone and chaulmoogra (89) and 38 with sulphetrone (87). The conclusion reached is that " although these observations on isoniazid in the treatment of leprosy cover only twenty-three cases, yet the marked improvement observed in a good proportion of the cases, particularly the highly infected ones, given some solid ground for concluding that this drug has a definite therapeutic value in such cases. It will further be noted that the results obtained with isoniazid have been approximately as favourable as with other forms of treatment. It deserves a more extensive and prolonged trial, by itself and also in combination with chaulmoogra oil intradermally ". ERNEST MUIR.

MARKIANOS, J.

" The Action of Isoniazid in the Treatment of Leprosy ". Bull. Soc. Path. Exot. 1954, Vol. 47, No. 1, 32-4.

The author treated with isoniazid 2 patients having combined leprosy and tuberculosis with no amelioration of the tuberculosis but with slight improvement of the leprous lesions. In 13 patients with leprosy alone, of the macular type, there was some improvement, especially in recent cases. In 25 more advanced lepromatous cases there was slight improvement, and the author considers that this drug may be used when there is intolerance of the sulphones. In all, 45 patients were treated. Three of these were attacked by jaundice which lasted 2 to 3 months, and there were various other reactionary complications requiring withdrawal of the drug. These were observed most commonly when the daily dose was increased from 150 mgm. to 300 mgm. and maintained at that level. (The author does not use the modern form of classification.)

ERNEST MUIR.

CARTER, F. S.

" Primary Tuberculosis in African Children and the Value of Isoniazid in Treatment ". East African Med. J., 1954, June, Vol. 31, No. 6, p. 265.

In this paper the author considers that tuberculosis has been introduced into Kenya comparatively recently and that the native population has had little time to develop any natural resistance. The disease, therefore, is often not localised and the primary infection does not lead to a healing focus but to dissemination and death. Mantoux tests in over a thousand children under 10 years in the medical wards of the King George VI Hospital, Nairobi, gave only 11.5% positives and, in addition, 31 children with rapidly progressive tuberculosis had a negative Mantoux test. In the present study 41 children with positive Mantoux tests, and showing evidence of an active primary tuberculosis infection, were studied. The majority were obviously sick, with marked constitutional disturbance, and local signs are described. Thirty-eight children were specially studied, some treated with Isoniazid and some without. The effect of the treatment on the temperature, on the weight, the sedimentation rate and radiological findings and also on the general clinic condition, are recorded.

The following conclusions were drawn:—

1. Thirty-eight African children with active primary tuberculosis were observed for periods varying from four to fourteen months.

2. It was found that the severity of the disease is greater than that usually seen among children in the United Kingdom, and the

outlook much less favourable. Fever and mental apathy were prominent features. All the deaths occurred within three months of the first symptoms of the primary infection.

3. Radiologically, there was enlargement of the hilar glands in 40 out of 41 children (97.5%), and it was to a considerable degree in 24 of them (58%).

Absorption collapse or collapse-consolidation was observed in 28 children (68%). Clinical progress outstripped radiological evidence of improvement almost invariably.

4. The value of isoniazid therapy was investigated.

5. Twenty-two children were treated with isoniazid (Rimifon) and sixteen acted as controls. Those receiving isoniazid gained weight more quickly than the controls, and their temperature fell to normal more rapidly.

6. When the disease ran a benign course, those receiving isoniazid appeared to be restored to health more quickly than the controls, but the drug was not able to prevent dissemination of the disease. Two children developed suppurative tuberculosis cervical adenitis, one phlyctenular conjunctivitis, one tuberculous meningitis, one miliary tuberculosis, and two died from tuberculous bronchopneumonia. Three cases of tuberculous bronchopneumonia occurred among the controls.

It is probably unjustifiable to use isoniazid in the treatment of primary tuberculosis as the drug does not prevent the development of fatal complications, and a drug resistant organism is produced in a large percentage of patients when used by itself. It is suggested that isoniazid therapy should be reserved for use in conjunction with streptomycin when such complications occur.

7. The ultimate prognosis appears to be favourable if the child survives the first three months of the infection.

(Author's Summary)

CHAUSSINAND, R., VIETTE, M. & KRUG, O.

Action de l'Hydrazide de l'Acide Isonicotinique sur le rat infecté par le bacille de Stefansky. Annales de l'Institut Pasteur, **84**, p. 431, February, 1953.

The authors' conclusions are as follows:—

Thirty rats subcutaneously inoculated between 6½ and 7 months ago with suspensions of Stefansky's bacilli were treated for 16 days after the inoculation with isonicotinyl hydrazide, 0.76-1 mgm daily. The treated animals showed no clinical lesions. Histological examination showed slight lesions at the point of inoculation, and in the local lymph node, these lesions showing a few altered bacilli. Fifteen controls inoculated at the same time with the same dose,

but not treated, showed a classical picture of marked lesions at the point of inoculation and a massive lymphatic spread.

The interest of these results lies in the fact that previously no antibiotic or chemotherapeutic agent had been able to control the formation of the local lesion and the spread of this infection.

CHAUSSINAND, R., VIETTE, M. & KRUG, O.

Evolution de l'infection a Bacille de Stefansky chez le rat traité par l'Hydrazide de l'Acide Isonicotinique. Annales de l'Institut Pasteur, **85**, p. 398, Sept. 1953.

The authors' conclusions are as follows:—

Isonicotinic hydrazide given by mouth in doses of 0.75-1 mgm during a period of 10 months has not eliminated the disease produced by the subcutaneous inoculation of Stefansky bacillus. Nevertheless, the appearance of the local lesions and the lymphatic spread and visceral involvement when they occurred were seen to be much retarded, and the pathological lesions are less extensive and less marked than in the controls. On the other hand, the treatment with I.N.H. appears more effective if it is not started until the seventeenth day after inoculation.

CHAUSSINAND, R., GABBAI, A., DORENLOT, H. & VIETTE, M.

Action de l'Hydrazide de l'Acide Isonicotinique sur la maladie de Hansen. Bulletin de la Société de Pathologie exotique, **46**, p. 905, Nov.-Dec., 1953.

The authors' conclusions are as follows:—

Forty-four patients (31 lepromatous, 12 tuberculoid and 1 indeterminate) have been treated for between 3 to 12 months, some with INH alone, or with INH and DDS. The dose of INH varied and the highest was 8 to 12 mg per kilo body weight. INH is better tolerated, but less active than sulphones in leprosy. Its use alone cannot be recommended. In low doses the results are mediocre, and high doses are sometimes not tolerated, but results are better.

The interest of this product appears to be in its use together with sulphones in patients either in poor general condition or tolerating sulphones badly. A longer study of this combined treatment is desirable.

CHAUSSINAND, R.

" Therapeutique de la Lepre ". Extract from *La Revue du Practicien*, No. 21, of 21st July, 1954.

In this article Chaussinand reviews the development of modern treatment of leprosy and assesses the present position. The ground covered is familiar to most of our readers and does not lend itself to abstraction. The opinion is expressed that DDS constitutes without doubt a most powerful weapon against leprosy. The author

mentions and discusses briefly treatment with thiosemicarbazone, chaulmoogra oil, INH, streptomycin, PAS etc.

CHAUSSINAND, R. & TOUMANOFF, C.

"Cellular Reactions and Phagocytosis in Guineapigs Inoculated Intraperitoneally with Living and Dead Leprosy Bacilli". *Ann. Inst. Pasteur.* **85**, p. 713-23, Dec., 1953.

Inoculation of suspension of leproma was followed by an exudate containing first polymorphonuclears and then monocytes, the latter being either macrophages or lymphocytes. The reaction was the same in nature whether the bacilli were alive or had been killed by heat, but was sometimes more intense if the bacilli were alive. This less intensity in the case of the dead bacilli may follow some chemical change in the lepromatous tissue injected and may be due to the heating of the suspension. The polymorphonuclear reaction lasts only some 24 to 48 hours, but bacilli can often be found inside macrophages as long as 3 months later. Thus the natural immunity of guineapigs to human leprosy is due to their power to phagocytose the bacteria. ERNEST MUIR.

NEYRA-RAMIREZ, J.

"Study of the Action of BCG on the Leucocyte Formula and on Phagocytosis in the Peritoneal Exudate when Guineapigs are Inoculated with Living and Dead Rat Leprosy Bacilli". *Ann. Inst. Pasteur.* **86**, Jan. 1954.

Five guineapigs were vaccinated intradermally with BCG, and after 6 weeks all had become Mantoux-positive; 3 of these and 3 unvaccinated controls of the same weight were inoculated intraperitoneally with living rat leprosy bacilli. Likewise, the other 2 vaccinated animals and 2 unvaccinated controls were inoculated similarly with a suspension of rat leprosy bacilli which had been autoclaved for an hour. The peritoneal exudate was aspirated and studied for a period of 100 days.

First polymorphonuclears phagocytosed the bacilli, followed by monocytes which ingested and destroyed bacilli, and also destroyed both polymorphonuclears and monocytes containing bacilli. The rate at which this "autophagie" took place varied in the different groups. In the vaccinated animals it took 4 to 8 days with the living bacilli, and 4 to 6 days with the dead ones. In the unvaccinated controls it took 12 to 16 days with the living bacilli, and 12 to 14 with the dead. There was pyknosis of the nuclei of the polymorphonuclears in the animals inoculated with living, but not dead, bacilli, which may have been due to toxins either from the living bacilli or from the rat tissue. The more rapid autophagie in the vaccinated animals is taken as an indication of increase in the defence mechanism in animals which are naturally resistant to rat leprosy bacilli. ERNEST MUIR.

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