

NEW DRUGS FOR TRIAL IN LEPROSY

Apart from Chaulmoogra Oil and its derivatives, we have no remedy which has been acknowledged generally as of value in the treatment of leprosy, and in progressive cases of the lepromatous type, chaulmoogra has little or no effect. It is, therefore, with much interest that we turn our attention to new drugs which give hope of improvement. The many points of similarity between tuberculosis and leprosy make it natural that any drug found of value in the one disease should receive a careful trial in the other.

Promin and diasone have the effect of suppressing tuberculosis in experimental animals, but their toxicity has limited their use in the human subject in tuberculosis. However, favourable results have been obtained at least up to a point in leprosy. It has been suggested that the failure to influence tuberculosis in the human subject as compared with experimental animals is the greater chronicity of the disease in the latter and the consequent tendency of necrosed tissues to shut off the infection from the circulation. Leprosy is even more chronic than tuberculosis, but on account of its lesser toxicity, necrosis is less common. It may be on that account that the effects in leprosy are more favourable.

Penicillin has been reported as not of value in tuberculosis, but we include below two reports from Dr. Wharton, of the Mahaica Leprosy Hospital, British Guiana, showing the valuable results obtained in 15 cases. Recent reports show that streptothricin and streptomycin, derivatived, like penicillin, from moulds, have bacteriostatic effect on the tubercle bacillus, both *in vitro* and in experimental animals. The results of these preparations in leprosy should be of great interest.

Lastly, a report comes from Madagascar of a glucoside derived from a plant common in many parts of the tropics. Its reported action in leprosy appears to be somewhat similar to that obtained with promin and diasone.

It will be noticed that in the four out of these five drugs which have already been used in leprosy the effects are most striking in advanced cases. No results are as yet available in early lepromatous cases such as would be expected if the action were directly on the lepra bacillus itself. However, such results might be slow to appear, as it is known that even dead acid-fast bacilli will linger for a considerable period in the tissues without losing their acid-fastness. Whatever favourable results have been obtained at least indicate lines along which investigations

should be developed and raise the hope that further advances in the treatment of leprosy may be expected soon.

The following are short reports on each of these drugs :

Promin

Faget and his colleagues¹ in the National Leprosarium, Carville, U.S.A., after using this drug for some two years, came to the following conclusions : ' Promin is the sulfonamide drug which thus far seems to possess to the greatest extent some chemotherapeutic properties against leprosy. While no direct evidence of a specific bacteriostatic or bacteriocidal action against *M. leprae* has been demonstrated, it has been observed that promin appears capable of inhibiting the progress of leprosy in a considerable percentage of cases. As yet no case of leprosy has become arrested under its influence. It is found that promin can be safely administered intravenously for prolonged periods provided the blood and urine are examined frequently. When these precautions are taken, toxic manifestations are relatively rare and mild. The most important of them, hemolysis, if recognised early, is usually controllable and not a cause for discontinuance of treatment. Further experimental and clinical studies on the treatment of leprosy with promin must be conducted before more definite conclusions can be drawn as to its therapeutic value. It is not claimed that promin is a specific for leprosy, but in the writer's estimation it is an advance in the right direction in the therapy of this disease. Promin can be considered to have opened a new avenue in the chemotherapy of the mycobacterial diseases. It is hoped that further synthesis of sulfa compounds may produce a substance which will succeed in saving countless lives in this still dark field of medicine.'

Diasone

Favourable results have been obtained in the treatment of certain forms of leprosy by the administration of a synthetic preparation called Diasone². It is a white powder which may be given by the mouth or (as first used by the writer) may be dissolved in normal saline and, after filtration, injected intravenously. Two chief dangers have to be guarded against : a tendency to produce haemolysis and secondary anaemia, especially at the beginning of the treatment, and an inflammatory reaction in the lesions. To guard against these dangers, it is necessary to make frequent blood tests, preferably red cell counts, but if that is not possible, the haemoglobin index may be relied on. Also, before each administration, the patient should be carefully examined. During the first few weeks, especially in

weak cases, it is an advantage to keep the patient in hospital and have the temperature taken and the urine examined for albumen.

If no intolerance is shown, diasone should be given on alternate days three times a week. The initial dose was generally 0.6 g., rising to 2.6 g. when given intravenously; 1 g. was dissolved in 3 cc. of sterile normal saline and the solution was filtered through three layers of sterile gauze. In patients with Hb. index of less than 7.1, the maximum dose was 1.3 g. and ferrous sulphate 4 grains twice a day. Injections of liver extract were given to patients who showed progressive anaemia, and diasone was either stopped temporarily or the dose reduced.

The most marked results are in advanced lepromatous cases, with ulcerating lesions of the skin and nose and advancing inflammatory condition of the eyes. In many cases these lesions heal up rapidly, the temperature becomes normal and the general condition of the patient improves. In less advanced cases nodules become flattened or liquify, burst, and dry up rapidly. There is a general feeling of well-being, and patients who have been bed-ridden are, in many cases, able to become active and engage in work. No cases have so far become bacteriologically negative. This drug is still in the experimental stage and is not yet available for general use.

Streptomycin

The *British Medical Journal* reports the use of this new antibiotic in tuberculosis³. "Recently, two promising compounds, streptothricin and streptomycin, have been isolated by Waksman and others from certain species of soil actinomycetes. They resemble each other in many respects, but streptomycin is likely to prove the more valuable of the two. It is derived from *Actinomyces griseus*, grown under certain conditions. The chief promise of these compounds lies in their action on the Gram-negative bacilli, many of which are resistant to both sulphonamides and penicillin. The most interesting of all applications of streptomycin, however, is its possible use against tuberculosis; . . . it inhibits the growth of tubercle bacilli *in vitro*. Recently, Feldman and Hinshaw have described a trial on tuberculosis in guinea-pigs similar to their previous trials with promin. Guinea-pigs were inoculated with virulent bacilli and treated with doses of up to 6,000 units daily for sixty days. At the end of this time there was widespread tuberculosis in untreated control animals, while in the treated animals it was hardly detectable microscopically; viable bacilli, however, were usually still present. These results are interpreted as showing that the anti-

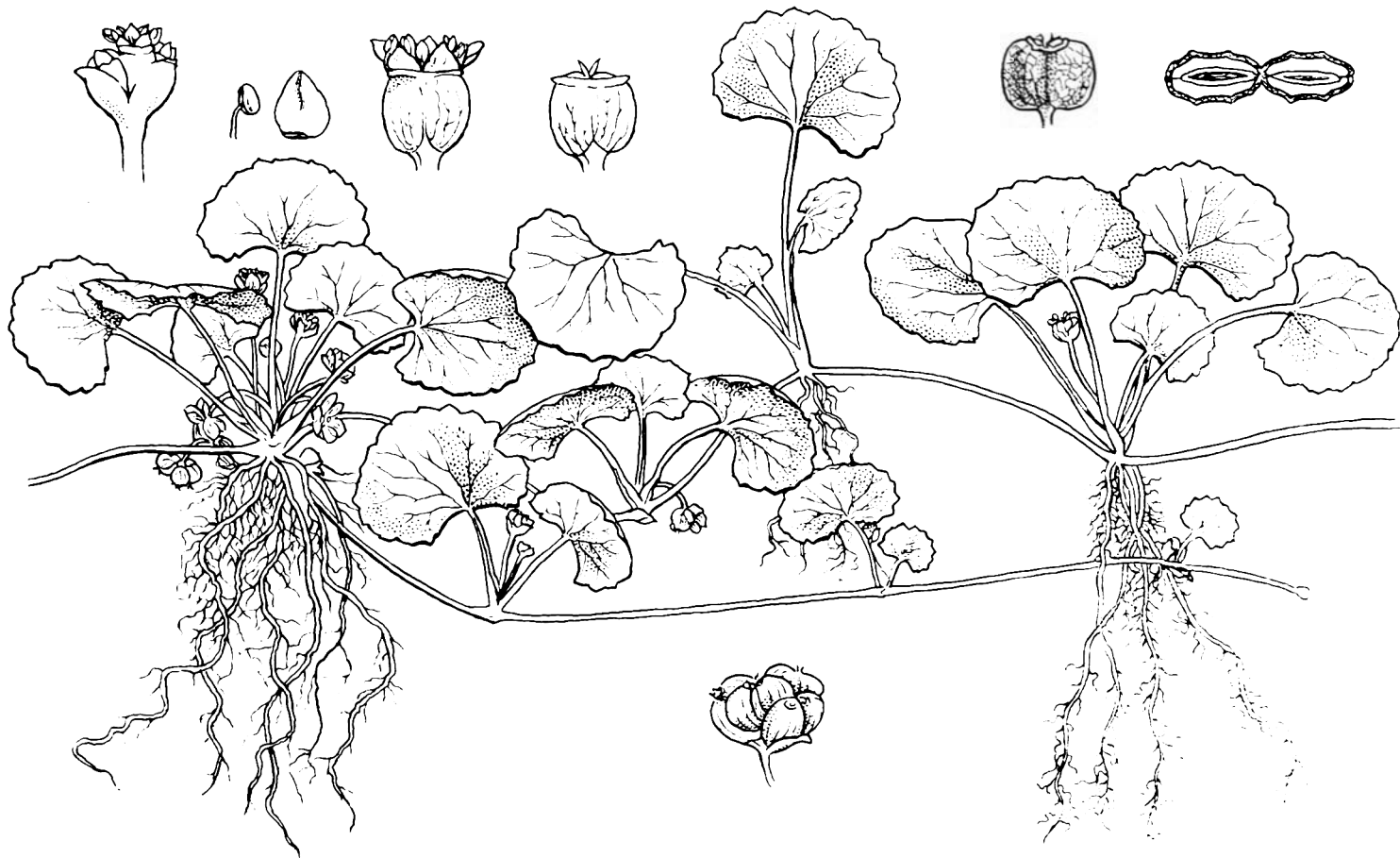
tuberculous activity of streptomycin is comparable with that of promin and similar compounds. . . . When streptomycin and streptothricin become more widely available in large enough quantities their clinical applications will deserve careful study."

Asiaticoside

*The Lancet*⁴ reports the use of this drug in the treatment of leprosy. "A new method of treating leprosy is reported from Madagascar, according to the French Mission of Information. Dr. Grimes and Dr. Pierre Boiteau, who are responsible for the study, have been using a glucoside extracted from *Hydrocotyle asiatica*, an umbelliferous plant growing on the island. As far back as 1937 they had been experimenting with this plant, but at that time the chemical composition of extracts was not fully known, and therapeutic dosage was too close to toxic dosage for safety, though results were encouraging. In 1938, Boutemps, working at the leprosy laboratory at Antananarivo, isolated from the plant a new glucoside, which he named "asiaticoside"; this proved to be active and much less toxic than previous preparations. It is insoluble in water, and barely soluble in alcohol, but dissolves well in pyridine. Its chemical nature is being further studied by Devanne and Razafimahery. Boiteau has succeeded in making a solution which can be given by injection, and results so far are said to be remarkable. Ocular lesions are cured at once if treated before the posterior chamber is affected. Diffuse infiltrations disappear, lepromas break down and fill with fluid, burst, and afterwards scar up. Acute digital lesions and perforating ulcers heal completely. Anaesthesia and nervous lesions take a long time to improve, and recovery is equally slow in the muscles, but nevertheless, many patients treated in Madagascar have already reached the stage of active reablement. Boiteau and Grimes consider that the glucoside probably acts by dissolving the waxy capsule of the lepra bacillus, thus exposing it to attack by the defensive agents of the body and by other drugs." The Director of the Royal Botanic Gardens, Kew, has kindly supplied further information about the plant referred to, and the illustration, a copy of which is attached. He writes: "*Hydrocotyle asiatica* L, now known as *Centella asiatica* (L) Urban, is very widely and generally distributed throughout the Tropics and sub-tropics of both hemispheres. It is a variable species, and is believed to consist of a number of varieties, and these may possibly vary in their glucoside-content."

(Penicillin)

Copies of two Reports on trials of Penicillin in leprosy addressed to the Secretary, The Board of Penicillin Control,



Centella asiatica (L) Urban (*Hydrocotyle asiatica* L).

Medical Department, have been received from Dr. L. H. Wharton, Medical Superintendent, Mahaica Leprosy Hospital, British Guiana, dated respectively April 30th and June 4th, 1945.

First Report.—Six cases of leprosy who have received a short course of Penicillin treatment. The sodium salt of Penicillin was used; each patient received 100,000 units, divided into 5,000 unit doses, by intramuscular injection every three hours. The cases selected were advanced Lepromatous (L-3) cases, who were gradually getting worse, and who had developed many complications of leprosy, viz., chronic ulcers, ophthalmic complications and repeated attacks of lepra fever.

Only one patient complained of any ill effects from Penicillin. This patient, after receiving 50,000 units, complained of vertigo, headache, nausea, and his pulse became irregular. Stimulants were given and he recovered, and asked to be allowed to finish the course of treatment. He received a further 50,000 units without any ill effects. None of the patients complained of pain at the site of injection. The patients were all co-operative, and a marked improvement in their morale was seen after 24 hours' treatment. I give below a detailed report on each case :

Case 1. A.B. Female 28. Mixed race. Advanced L-3 leprosy, with extensive chronic ulcers of both legs. Angry red Lepromatous infiltration of the face and forearms, skin section showing streptococci and staphylococci. Blood sedimentation index, 42.5. Leprosy smears before treatment; skin and nose M/1 (M denoting more than 10 lepra bacilli in each field examined).

After Penicillin: The red lepromatous patches on the face and forearms had subsided completely, and there was marked reduction in the raised infiltrations. The chronic ulcers had lost their slough and showed healthy granulations. The leprosy smears showed no change from skin and nose, but the blood sedimentation was reduced to 11.5.

Case 2. L.H. Female 28. Negro. Advanced L-3 case. Numerous nodules on face and forearms and legs, and chronic ulcers of both legs. Lepromatous infiltration of both eyes, badly impaired vision. Blood sedimentation test 69.5. Skin and nose M/1.

After Penicillin: The nodules on face, forearms, and legs were greatly reduced. The oedema of the face disappearing completely. The ulcers of the legs were much improved, had lost the slough, and showed healthy granulations. The vision had greatly improved, and the patient stated she could now distinguish persons at a far distance, which she could not do before. Blood sedimentation test was reduced to 40, but leprosy smear tests remained the same.

Case 3. W.H. Male 39. Negro. Advanced L-3 case. Ulcerating nodules of face, both hands, chronic ulcers both legs. Repeated attacks of lepra fever. Blood sedimentation 37.5. Skin and nose M/1.

After Penicillin: Marked improvement in all ulcers, all redness and oedema of face subsiding. Blood sedimentation 20. Leprosy smears remained the same.

Case 4. J.C. Male 19. Chinese. L-3 case. Numerous nodules on face, forearms, and legs; in an attack of lepra fever temperature 101. Chronic ulcers both legs. Blood sedimentation 35. Skin and nose M/1.

After Penicillin: The temperature became normal after 24 hours'

treatment. There was marked improvement in the nodules, redness subsided. The chronic ulcers of legs had taken on a healthy appearance. Blood sedimentation reduced to 26. Leprosy smears remained the same.

Case 5. B.B. Male 15. Mixed race. Advanced L-3. Extensive nodules of face, forearms, legs. Much oedema of face. Frequent attacks of lepra fever. Lepromatous infiltration of both eyes, with marked conjunctivitis in one eye. Vision greatly impaired. Blood sedimentation 57. Skin and nose M/1.

After Penicillin: The oedema of the face subsided and there was marked reduction of nodules. The conjunctivitis had cleared up completely and the patient stated that the vision has greatly improved. The ulcers of the legs had taken on a healthy appearance. Blood sedimentation reduced to 35.5. Leprosy smears remained the same.

Case 6. J.S. Male 30. Negro. Advanced L-3. Ulcerating nodules of nose, face, forearms, hands, and legs. Loss of vision in one eye from lepromatous infiltration, and the other eye showing signs of infiltration, impaired vision, and conjunctivitis. Frequent attacks of lepra reaction. Blood sedimentation 43.5. Skin and nose M/1.

After Penicillin: There was marked improvement in all nodules and ulcers, and great improvement in the eye. Conjunctivitis had subsided completely and the patient stated the vision was much better. Ulcers had taken on a healthy appearance. Blood sedimentation reduced to 26.5. Leprosy smears remained the same.

Conclusion

(1) 100,000 units of Penicillin given to six patients over a period of 60 hours has shown marked improvement in the complications of leprosy.

(2) The above dose is not bacteriostatic or bacteriocidal to the leprosy bacillus.

(3) The blood sedimentation test showed marked improvement in all patients.

(4) I consider that this experiment shows promising results, but I think that Penicillin should be given in larger doses over a period of five days.

Second Report.—Nine patients suffering from advanced lepromatous leprosy—L-3 cases—were treated with sodium salt of Penicillin. Three patients received 400,000 units each, given in 10,000 unit intramuscular injections every three hours. Six patients received 200,000 units each, given in 5,000 units intramuscularly every three hours.

It was noticed that all the patients experienced a marked increase in appetite and complained of a feeling of drowsiness while under treatment.

None of the patients showed a rise in temperature, nor did anyone complain of undue pain at the site of injection.

The patients were most co-operative and took a keen interest in the treatment.

I now give details of each case.

Patients who had received 400,000 units

Case 1. C.H. Male, 28 years. Mixed race. L-3 leprosy. *Before*

Penicillin: This patient was covered with large nodules and extensive deep ulcers of both legs. He had repeated attacks of lepra reaction and was gradually getting worse. The nodules on the nose, face, and hands were ulcerating. Blood sedimentation was 48. Leprosy smears: Nose and skin were positive, bacilli being recorded as M/1 (M denoting more than 10 bacilli in each field).

After Penicillin: The ulcerating nodules of the nose, face, and hands had healed completely. The oedema of the legs had decreased, and the large, deep sloughing ulcers of both legs were clean, healthy, and granulating up from the craters. The patient felt very much better physically and there was marked improvement in his mental outlook. Blood sedimentation was 22.5. Leprosy smears: Nose and skin remained M/1. were M/1.

Case 2. J.J. Female; 25 years. East Indian. Suffering from advanced lepromatous leprosy—L-3. Recent repeated attacks of lepra reaction. Extensive nodules of face and nose, arms, forearms, and legs. Nodules on face, nose, and legs breaking down and ulcerating. Oedema of face and legs. Gradually getting worse. Depressed mentally. Blood sedimentation was 60. Leprosy smears: Nose and skin were M/1.

After Penicillin: Marked reduction in oedema of face and leg. Ulcerating nodules of nose, face, and legs completely healed. Marked improvement in physical and mental condition. Blood sedimentation was 31.5. Leprosy smears: Nose and skin remained M/1.

Case 3. L.P. Female, 18 years. Negro. *Before Penicillin*: Advanced L-3 leprosy, extensive nodules of face, arms, forearms, and legs. Small chronic ulcers of both legs. Oedema of face and legs. Early lepromatous infiltration of both eyes. Gradually getting worse. Blood sedimentation was 52.5. Leprosy smears: Nose and skin were M/1.

After Penicillin: Marked reduction of oedema of face and legs, with complete healing of chronic ulcers of legs. Marked improvement in general physical condition. Blood sedimentation was 21. Leprosy smears: Nose and skin remained M/1.

Patients receiving 200,000 units

Case 4. H.C. Male, 32 years. Mixed race. *Before Penicillin*: Advanced L-3 leprosy. Extensive small nodules of face, nose, arms, forearms, hands, and legs. Chronic ulcers both legs. Oedema of face and legs. Lepromatous infiltration of both eyes, impaired vision, frequent attacks of pain in both eyes. Patient very depressed mentally, getting worse physically. Blood sedimentation was 56.5. Leprosy smears: Nose and skin were M/1.

After Penicillin: Marked improvement in oedema of face and legs and healing of ulcers of legs. Pain in eyes considerably diminished and improvement of vision in one eye. Marked improvement in mental and physical condition. Blood sedimentation was 20. Leprosy smears: nose and skin remained M/1.

Case 5. S. Male, 24 years. East Indian. *Before Penicillin*: Advanced L-3 leprosy. Large nodules of face, arms, forearms, hands, and legs. Ulceration of nodules on face and hands, and chronic ulcers of both legs. Oedema of face and legs. Repeated attacks of lepra reaction. Gradually getting worse. Blood sedimentation was 44. Leprosy smears: Nose and skin were M/1.

After Penicillin: Marked improvement in oedema of face and legs. Marked healing of ulcerating nodules and ulcers of legs. General physical condition much improved. Reduction of size of nodules of the face. Blood sedimentation was 23. Leprosy smears: Nose and skin remained the same.

Case 6. R.C. Male, 24 years. Negro. *Before Penicillin*: Advanced L-3 leprosy. Extensive nodules of face nose, arms, forearms, hands, and leprosy. Extensive nodules of face, nose, arms, forearms, hands, and legs. Nodules ulcerating on face and nose. Chronic ulcers of legs.

Lepromatous infiltration of eyes with impaired vision. Gradually getting worse. Blood sedimentation was 25.5. Lepra smears: Nose and skin were M/1.

After Penicillin: Healing of ulcerating nodules on face, nose, and hands. Ulcers of legs healthy and greatly improved. Vision improved. Marked improvement in general physical condition. Blood sedimentation was 10. Lepra smears: Nose and skin M/1.

Case 7. B. Female, 27 years. Portuguese. *Before Penicillin:* Advanced L-3 leprosy. Repeated attacks of lepra reaction. Extensive nodules on face, forearms, hands, and legs. Red angry patches of infiltration of skin of face and forearms. Chronic ulcers of legs with oedema. Gradually getting worse. Blood sedimentation was 51.5. Lepra smears: Nose and skin were M/1.

After Penicillin: Marked improvement in acute reaction of face and forearms, reduction of oedema of face and legs. Chronic ulcers of legs showed marked improvement. General physical condition greatly improved. Blood sedimentation was 24.5. Lepra smears remained M/1.

Case 8. M.A. Female, 33 years. Negro. *Before Penicillin:* Advanced L-3 leprosy. Extensive large nodules of face, forearms, and legs. Nodules undergoing reaction. Oedema of face and legs. Ulcerating nodules of legs. Blood sedimentation was 21.5. Lepra smears: Nose and skin were M/1.

After Penicillin: Marked reduction of oedema of face and legs, with healing of ulcers of legs. Acute reaction subsided completely. Marked improvement in general physical condition. Blood sedimentation was 9.5. Lepra smears: Nose and skin remained M/1.

Case 9. W. Male, 21 years. Negro. *Before Penicillin:* Advanced L-3 leprosy. Extensive large nodules of face, forearms, hands, and legs. Had lost left eye from nodule. Right eye had small nodule on cornea; greatly impaired vision. Chronic ulcers of leg. Gradually getting worse, very depressed mentally. Blood sedimentation was 51.5. Lepra smears: Nose and skin were M/1.

After Penicillin: Marked improvement in the general physical and mental condition. Healing of ulcers of legs. Slight improvement of vision in right eye. Blood sedimentation was 29.5. Lepra smears: Nose and skin remained the same.

Conclusion

(1) Penicillin given in total doses of 400,000 units is not bacteriocidal or bacteriostatic to bacillus lepra.

(2) It is of definite value in the complications of leprosy, especially in ulcerating nodules, lepra reaction, chronic ulcers, and inflammatory eye conditions.

(3) The marked improvement in physical and mental condition of the patient in L-3 leprosy would justify its use.

¹ *Int. J. of Lep.*, Vol. 11, p. 52.

² *Int. J. of Lep.*, Vol 12.

³ *Brit. Med. J.*, May 19, 1945, p. 706.

⁴ *Lancet*, March 17, 1945.