

THE TREATMENT OF TUBERCULOSIS IN LEPROSY PATIENTS

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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 leprosy 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 leprosy 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 nor 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 tuberculous 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 leprosy patients, it would be advantageous 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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