ACUTE AGRANULOCYTOSIS CAUSED BY TB1/698 (PARA-ACETAMIDOBENZALDEHYDE THIOSEMICARBAZONE)

JOHN LOWE

The use of TB1/698 in leprosy has been described by Hohenner (1949) Grosch and Kaliebe (1950) Walter (1950) Ryrie (1950) Schneider *et al* (1950) Vegas *et al* (1950) and Lowe (1952). The earlier reports dealt with one or a few cases treated for short periods. My previous report dealt with 126 cases treated for periods up to seventeen months.

The present report is not concerned with the value of TB1 in leprosy, which was dealt with previously. It is concerned with the occurrence of acute agranulocytosis during the administration of this drug.

Specific toxic effects of TB1. 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: but that is not the opinion of the majority.

The effects recorded included anorexia, headache, epigastric discomfort, vomiting, and other evidence of disturbed liver function; fever and rashes; a mild haemolytic anaemia; and agranulocytosis (rarely). Thus there is evidence of damage to the liver and to the bone-marrow.

In 146 cases treated for periods up to 21 months, the only serious toxic effect has been an acute agranulocytosis which has been seen in three cases, associated in one case with hepatitis and jaundice.

Case records.

(1) A young man, in good physical condition, with tuberculoid leprosy, was treated with T.B.1 50 mg. a day for the first week, 100 mg. a day for the second week, and thereafter 150 mg. a day. At the end of five weeks treatment, he appeared one morning complaining of malaise, and pain in the teeth. That afternoon his temperature was 103°F; he was ill and toxic, and his tooth sockets, tonsils, fauces, and the nail beds of the toes were acutely inflamed. An acute agranulocytosis was diagnosed and confirmed by blood examination, and intensive penicillin treatment was instituted,

1,000,000 units of procaine penicillin in oil being given each day. The clinical condition subsided in three days, except that small necrotic areas on the toes took several weeks to heal. The white-cell counts before treatment started and during and after this incident are shown in the accompanying table.

The striking features were a decrease of more than 90% in the total granulocytes; a decrease of 82% in the polymorphs, with a return to the previous figure in a week; and the almost complete disappearance of eosinophils, which had previously been very numerous (associated with filariasis due to Acanthocheilonema perstans), and their failure to reappear until the third week.

(2) A young African man in good physical condition, with mild leprosy, started T.B.1 treatment on February 9th, 1952; the dosage was 50 mg. a day for one week, 100 mg. a day for the second week, and 150 mg. a day for the third week. On the twenty-second day of treatment he felt unwell and feverish in the evening, and next morning he reported with a temperature of 101°F. Malaria was suspected, but a blood-film revealed acute agranulocytosis. T.B.1 was stopped, and 1 million units of penicillin was given and was repeated daily until recovery. Pentnucleotide was not available.

That afternoon the temperature rose to 105°F. There was no serious inflammation of the mouth or throat; there was a small septic focus on one foot at the site of a cut, and later a similar focus appeared on one hand.

A remittent fever continued for seven days, reaching its maximum, 106°F, on the second day and then slowly subsiding. During this time no serious local inflammation developed any where, and the general condition of the patient remained fair, but toxaemia was marked. The spleen became palpable on the fourth day.

At the eighth day the penicillin injections were stopped, but almost immediately the fever recurred and a widespread lymphadenitis developed, with suppuration of the femoral glands on both sides; this cleared up with further penicillin treatment and surgical drainage. Smears from the evacuated pus showed staphylococci. During this second period of fever the white cell count was high and many immature cells (myelocytes and metamyelocytes) appeared in the peripheral blood. Thereafter the patient made an uninterrupted recovery and has since been treated with diamino-diphenyl sulphone with no complications.

(3) A well nourished young man with moderately severe leprosy started treatment with TB1 on Jan. 29/1952, the dose being 100 mg. a day for three weeks, and 150 mg. a day thereafter.

On March 13th after six weeks treatment he became ill with some fever but no obvious cause. There was no local symptom of any kind, and the blood showed no malaria parasites. The polymorphonuclear count was low; agranulocytosis was suspected and daily blood counts were made; five days later agranulocytosis was definitely diagnosed, so TB1 treatment was stopped and penicillin treatment was instituted. During the next two days the fever fell, but the spleen and liver became enlarged, and jaundice developed. Later the fever subsided and the granulocytes returned, but the liver was enlarged down to the umbilicus, and was very tender. Later the jaundice became intense, although the patient's general condition remained good. All the usual laboratory tests for a toxic hepatitis gave positive results. During the next ten weeks, with no specific treatment, the hepatitis and jaundice slowly subsided. Treatment with diamino-diphenyl sulphone has just been started.

Period of T.B.1 treatment	**Case 1 5 weeks**	**Case 2 3 weeks**	**Case 3 6 weeks**	Notes
Total count before treatment	10,300	6,500	8,500	
Granulocytes ...	5,900	3,200	4,240	
Day of illness 1	3,300	1,800	4,800	In cases 1 & 2 TB1 treatment stopped.
Total count and granulocytes ...	500	180	1,100	In case 3 continued
Day 2	3,500	1,300	6,700	
	500	110	2,000	
Day 3	3,000	1,900	7,000	
	600	140	1,500	
Day 4	3,700	2,300	—	
	800	120	—	
Day 5	—	2,000	7,800	TB1 stopped in case 3.
	—	40	250	
Day 6	4,200	4,200	7,900	
	1,900	430	230	
Day 7	4,500	8,500	6,200	Many myclocytes & metamyclocytes present in case 2.
	1,900	2,550	120	
Day 8	6,000	10,000	5,600	,,
	600	5,230	450	
Day 9	6,500	10,100	8,400	,,
	2,900	6,190	1,600	,,
Day 10	6,000	17,900	7,300	,,
	2,200	12,940	2,400	
Day 11	6,200	15,600	—	
	3,000	12,000	—	
Day 12	—	17,800	—	
	—	13,600	—	
Day 18	—	7,100	—	
	—	5,250	—	

Discussion.

First arises the question of the diagnosis and causation. The white cell counts recorded in the table leave little doubt of the accuracy of the diagnosis. In case 1 the granulocytes fell from 5,900 to 500; in the second case from 3,200 to 40; and in the third case from 4,240 to 120. In all three cases the granulocytes began to increase within a few days of the cessation of TB1 treatment and of the institution of penicillin therapy. These three cases, and a fourth mild case recorded below, all occurred among 146 patients treated here with TB1; in some hundreds of other patients treated with other remedies for leprosy, no such case has been seen in several years. It appears certain that the cases were cases of agranulocytosis caused by the administration of TB1.

In all cases the agranulocytosis occurred during the first few weeks of treatment, and it is a striking fact that in 21 months treatment in 143 cases we have not seen agranulocytosis occurring later than the 6th week. It appears definite that agranulocytosis occurs early or not at all. This finding supports the idea, expressed by some other workers, that this agranulocytosis is an allergic rather than a toxic phenomenon, and is not attributable to the cumulative toxic action of the drug. Because there is another effective treatment (diamino-diphenyl sulphone), TB1 treatment has not been resumed since agranulocytosis occurred, although there is reason to believe that it could be resumed at low initial doses and with a gradual increase. In this connection, a fourth mild case in the present series may be quoted.

A young man with mild leprosy started TB1 treatment on March 20/1951. His granulocytes on that date numbered 2260 out of a total count of 4,700. After 23 days treatment with 100 mg. a day, he felt slightly unwell and had slight fever, and his granulocytes had fallen to 660 out of a total count of 3,000. Treatment was continued; three days later his granulocytes numbered 1430, and next day 2100; thereafter the number was steadily over 2000. This was apparently a mild agranulocytosis, which once again occurred in the first few weeks of treatment, and which subsided in spite of the continuance of TB1. Further, he has now completed 15 months treatment with no sign whatsoever of recurrence of the agranulocytosis. One would perhaps not recommend the continuance of TB1 treatment in an established case of agranulocytosis, but the above facts throw light on the causation and nature of agranulocytes, and suggest an allergic and not a true toxic phenomenon.

Nevertheless, as is well known, acute agranulocytosis can be very fatal, and our finding of 3 cases in 146 treated means that

the danger is a very real one. In cases 1 and 2, prompt diagnosis and penicillin treatment quite possibly saved the patient's life. The findings in case 2 indicated the occurrence of an acute staphylococcal septicaemia; probably a similar factor was present in the other cases.

Regarding diagnosis. Only in case 1 was there inflammation of the mouth and throat which are the classical signs of acute agranulocytosis. In cases 2 and 3 there were no localising signs to begin with, but merely fever with chills which naturally suggested malaria in this malarious country. In all three cases the agranulocytosis was detected in the thin and thick blood films prepared for examination for malaria parasites. In these films agranulocytosis is best detected by the use of the 2/3rd objective and a high power eye piece. These facts emphasise the importance of keeping an open mind and being prepared to find something quite different from what is expected, and of examining specimens with the low power of the microscope before using the oil-immersion lens.

One may formulate a general principle. In patients receiving treatment with thiosemicarbazones, any fever occurring during the first few weeks of treatment should be regarded with grave suspicion, and the blood should be examined for evidence of agranulocytosis.

Finally, regarding treatment of agranulocytosis, it may be said that penicillin in adequate doses has given very satisfactory results. If infections can be controlled, the granulocytes will look after themselves. No pentnucleotide was available, and none appeared to be needed. The speed of recovery from agranulocytosis under penicillin treatment was very striking in all three cases. In all three cases the granulocytes had returned in considerable numbers, with counts over 2000, within 9 days of the institution of penicillin treatment.

The hepatitis seen in one of the three cases was apparently a toxic hepatitis showing little or no connection with the agranulocytosis which accompanied it. It took many weeks to subside. Hepatitis has been recorded as a not infrequent toxic effect of TB1.

Summary and conclusions.

In 146 patients with leprosy treated with TB1 three severe and one mild case of agranulocytosis have been seen. In all four cases, the agranulocytosis occurred between the third and the sixth weeks of treatment. In the three severe cases, typical findings in the mouth and throat (" agranulocytic angina ") were found in only one. The symptoms were of fever with chills and strongly suggested malaria. In one case a staphylococcal septicaemia was present. Probably a similar factor caused the fever in the other two.

The total and differential counts before TB1 treatment and during the attacks of agranulocytosis are presented, and show a marked fall in granulocytes, the lowest figure recorded being 40 per cubic millimetre. The cessation of TB1, and the initiation of penicillin therapy was promptly followed by a fall in the temperature and the return to normal of the granulocyte count.

The findings are interpreted as indicating that the agranulocytosis was caused by TB1 and that it is an allergic rather than a true toxic phenomenon, for no case of agranulocytosis has been seen in the many patients who have had from 2 to 21 months continuous treatment with TB1, or who have been treated with sulphone.

The occurrence of such a serious complication of TB1 therapy in 3 of 146 cases treated indicates that the treatment can be used with safety only where adequate facilities for the detection and treatment of agranulocytosis are available. Every fever occurring during the first few weeks of TB1 treatment should be viewed with grave suspicion, and the blood should be properly examined for agranulocytosis. However the excellent response to treatment for agranulocytosis seen in all three cases indicates that, with proper facilities, TB1 treatment is not too dangerous to use.

The danger however is real, and the scope for TB1 treatment of leprosy must be a limited one, for in many countries where leprosy is common, medical and laboratory supervision of treatment is often difficult and sometimes impossible. For use in such areas, sulphone treatment is considered much safer. Moreover there is no clear indication that TB1 treatment is more effective than sulphone, though there are cases in which it is better tolerated.

Acknowledgments.

Thanks are due to Miss F. McNulty, Laboratory Superintendent, for the white-cell counts, and to the Inspector-General of Medical Services (Dr. S. L. A. Manuwa) and the Leprosy Adviser (Dr. T. F. Davey) for permission to publish.

REFERENCES

GROSCH, W., and KALIEBE, H. J. (1950) Zbl. Haut u. GESCHL-Kr. **9** p.1.

HOHENNER, K. (1949) Med. Klin. **44** p.1378.

LOWE, J. (1952) Lancet I p.436.

RYRIE, G. A. (1950) Lancet II p.286.

SCHNEIDER, J., LAVIRON, P., LAUREL, L., BASSET, A. (1950) Bull. Soc. Path, exot. **43** p.733.

VEGAS, M., CONVIT, J., MEDINA, J. A., DE BLOMENFIELD, E. (1950) Int. J. Leprosy, **18** p.451.

WALTER (1950) Z. Hals,—Nas,—u. Orenheilk **2** p.218.