TABLE II.—Distribution of Serum Levels following 600,000 Units of Benzethacil Intramuscularly

Serum Penicillin Levels (Units/ml.)	Time After Injection												
	3 Hrs.	6 Hrs.	24 Hrs.	48 Hrs.	72 Hrs.	5 Days	7 Days	10 Days	14 Days	17 Days	21 Days	24 Days	28 Days
0.10-0.15	4	3	2	1									
0.075-0.099	1	3	2	2	5								
0.05-0.074			2	3	10	1	1						
0.03-0.049					3		8						
0.02-0.029					1	2	7	1	1				
<0.02. No detectable level							2	5	6	7	6	8	3
										5	5	2	5
Total observations ..	5	6	6	6	19	3	18	13	16	12	11	10	8
Range	0.130/ 0.075	0.115/ 0.075	0.115/ 0.070	0.110/ 0.050	0.090/ 0.020	0.050/ 0.035	0.050/ <0.02	0.030/ <0.02	0.040/ <0.02	0.025/ <0.02	0.020/ <0.02	0.025/ <0.02	0.025/ <0.02
Mean	0.104	0.097	0.085	0.076	0.067	0.042							

Though small zones of inhibition were sometimes found at levels of less than 0.02 unit of penicillin, any serum showing less than this level was regarded as showing no detectable amount.

In Table III it is shown that assayable penicillin levels may appear only intermittently in some subjects. This phenomenon is not surprising when the insoluble nature of the preparation and the long duration of action are considered.

TABLE III.—Cases Showing Intermittent Penicillin Levels

Subject No.	Days After Injection							
	3	7	10	14	17	21	24	28
1	0.045	0	0	0	0.020	0.020	0.025	0.025
2	0.075	0.030	0	0.040	0.025	0	0.020	0
3	0.080	0.025	0.020	0	0	0.020	0.020	0.020
4	0.050	0.035	0	0.025	0.020	0	0.020	0.020
5	0.020	0.025	0	0.025	0.020	0.020	0.025	0

Discussion

This substance is a most interesting addition to the variety of penicillin preparations now available for therapeutic use. It is as yet too early to do more than suggest what place it may come to occupy in the treatment of disease. Venereal disease, since default from treatment is relatively common, would seem to be a promising field for trial. O'Brien and Smith (1952) have reported on the efficacy of this substance in the treatment of gonorrhoea, while preliminary results in the treatment of syphilis (Roberts, personal communication, 1952) have been said to be highly encouraging.

The prophylaxis of haemolytic streptococcal infection in patients who have suffered from rheumatic fever may be improved by the use of benzethacil. Stollerman and Rusoff (1952), who treated 135 convalescent rheumatic children, concluded that in most cases a single injection of benzethacil will clear the throat of haemolytic streptococci, and that with continued administration at fortnightly intervals there will be no recurrence of the carrier state. Unfortunately, low intermittent penicillin levels provide the optimum conditions for the emergence of drug-resistant organisms, and it is possible that the wide use of benzethacil would increase the magnitude of this problem.

The incidence of sensitization to this preparation is not yet known; but theoretically it may be low, owing to the long-continued exposure of the patient to low and at times intermittent penicillin levels. Preliminary data provided by O'Brien and Smith (1952) and Stollerman and Rusoff (1953) with combined series of 1,500 patients suggest that the incidence of significant penicillin reactions is not greater than 0.3%. In addition, O'Brien and Smith, in a study of four patients who developed urticarial manifestations within ten days of the injection, found that the reaction lasted only two to three days and cleared up whilst assayable penicillin was still present in the blood. However, in view of the unusual nature of the penicillin levels produced by

benzethacil further clinical study will be required before the danger of sensitization can be fully assessed.

We are grateful to Wyeth Incorporated, Philadelphia, Pennsylvania, for the supply of "penidural" benzethacil.

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CLINICAL TRIAL OF T.B.3 IN SURGICAL TUBERCULOSIS

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The thiosemicarbazones have been on trial in the treatment of tuberculosis for several years, principally in Germany, and a fair measure of success has been reported.

This report deals with a short clinical trial of one of the drugs, *para*-ethylsulphonylbenzaldehyde thiosemicarbazone (also known as T.B.3, "ethizone," and 8388), in eight patients suffering from tuberculosis of the spine or sacro-iliac joint whose organism was proved, or strongly suspected, to be resistant to streptomycin and P.A.S. We are concerned here mainly with the toxic effects of T.B.3, which in all our eight cases prevented the administration of the drug for long enough to reach any conclusions about its possible bacteriostatic effect on *Mycobacterium tuberculosis*.

Historical Survey

The use of thiosemicarbazones in tuberculosis was first described by Domagk *et al.* (1946). After trying many of these drugs they concluded that the most useful was *para*-acetamidobenzaldehyde thiosemicarbazone (thiacetazone; also known as T.B.1, "conteben," T.B.1/698); their report stimulated extensive clinical trials in Germany.

Donovick and Bernstein (1949) reported that T.B.1 was more active than P.A.S. but less active than streptomycin in early pulmonary infections, but its activity seemed to decline later in the disease. Karlson *et al.* (1949) found that in guinea-pigs T.B.1 and streptomycin, given together, were more effective than either given alone in ordinary therapeutic doses. Hurni (1949), however, working with mice, reported no additive effect of T.B.1 with either streptomycin or P.A.S. separately, though he found that T.B.1 did have some useful effect if given with both streptomycin and P.A.S. together. Heilmeyer (1949) reported good results in exudative lesions and in bone and joint infections. He noted a frequent fall in the erythrocyte sedimentation rate, which, however, did not correspond to any clinical improvement in the disease. He also recorded many toxic reactions, including liver and kidney damage and anaemia.

Hinshaw and McDermott (1950) and Mertens and Bunge (1950) reviewed German results in 10,000 cases. These workers confirmed the activity of T.B.1 against *M. tuberculosis*, but were unable to reach a definite conclusion about the clinical efficacy of the drug, since the trials had been conducted in Germany at a time when the general nutrition of the patients and the facilities for the general treatment of the disease were constantly improving. Toxic symptoms, consisting mainly of digestive disturbances and albuminuria, were fairly common, while profound anaemia developed occasionally after long courses of this treatment. A further possible toxic effect is mentioned by Stadler and Weissbecker (1951), who report a case of transient Cushing's syndrome in a patient receiving T.B.1.

As early as 1949 Hoggarth *et al.*, reporting trials of about 100 thiosemicarbazones and allied substances in infected mice, stated that T.B.3 seemed to be the most effective of these. In 1950 Hoggarth and Martin showed that T.B.3 was superior to P.A.S., though less effective than streptomycin. Martin and Stewart (1950), however, found T.B.3 superior to streptomycin in the early stages of the disease, but this relationship became reversed in more advanced cases. Bavin *et al.* (1950) and Hamre *et al.* (1950) agreed with other workers that T.B.3 was a more effective agent than T.B.1 in experimental mouse tuberculosis.

Rees and Robson (1951) showed that in experimental corneal tuberculosis T.B.3 with streptomycin was more effective than T.B.3 with P.A.S. or streptomycin with P.A.S. Ross *et al.* (1951) recorded encouraging effects from T.B.1 in conjunction with streptomycin and P.A.S. in human renal tuberculosis, but suggested that T.B.3 might be more efficacious and less toxic.

Little seems to be known about the possible toxic effects of T.B.3 in man. Francis *et al.* (1950) showed in monkeys that a dose of 500 mg. per kg. body weight twice daily produced fatty degeneration of the liver, and that 500 mg. per kg. once daily produced no toxic effects. The therapeutic value of this lower dosage in experimental tuberculosis was about half that of 40 mg. of streptomycin per kg. daily. This is equivalent to comparing a dosage in an average man of 3 g. of streptomycin daily with over 30 g. of T.B.3. From the known toxicity of the thiosemicarbazones such high doses in man would clearly be dangerous. Siebenmann and Zubrys (1952) have shown that the haemolytic anaemia produced by T.B.1 in mice does not occur with T.B.3. Spinks (1951) has shown that T.B.3 in mice and dogs produces blood levels four times as high as the same dosage of T.B.1. Since T.B.3 appears to be a more effective substance in the treatment of tuberculosis than T.B.1, it seems reasonable to hope that an effective blood level can be maintained on T.B.3 with less danger of toxic signs than on T.B.1.

Clinical Material

It was decided to conduct a limited clinical trial of T.B.3 in selected cases of bone and joint tuberculosis whose lesions were failing to respond satisfactorily to other

forms of treatment. All these patients were appropriately splinted and on a general sanatorium routine in hospital, and all had received appropriate surgical treatment where indicated. All were receiving daily 1 g. of dihydrostreptomycin and 15 g. of P.A.S. Three had developed proved resistance to one or both of these drugs, and in the other five the clinical progress led us to believe that such a resistance must be developing, though we were not able to prove this. In six of the eight patients the lesion was proved to be tuberculous; in one there was histological evidence but no bacteriological proof of tuberculosis; in the eighth the clinical and radiological condition was typical though there was no histological or bacteriological proof of its tuberculous nature.

Dosage.—The first four cases started on 50 mg. of T.B.3 a day and the dose was increased gradually over a period of a few weeks to the maximum of 200 mg. a day in divided doses. The later cases started on 100 mg. a day, and the dose was raised more rapidly to 200 mg. a day. This is the dosage advised by the makers, who warn against exceeding 250 mg. a day.

Routine Investigations.—The following investigations were carried out in all cases: daily urinalysis, weekly haemoglobin estimation, red-cell and white-cell counts, and a fortnightly or monthly erythrocyte sedimentation rate. Blood-sugar estimations and glucose-tolerance curves were done in five cases.

Case Records

Case 1.—A woman aged 30. Tuberculosis of left sacroiliac joint, onset summer, 1948; not proved. Recurrent sinuses despite streptomycin and P.A.S. Arthrodesis October, 1950. Recurrent wound breakdown. T.B.3 was given with streptomycin and P.A.S. from May 28 to August 7, 1951, when intermittent albuminuria and vomiting led to its discontinuation. E.S.R. rose during the course and haemoglobin fell from 102% to 74%.

Case 2.—A boy aged 9. Tuberculosis of dorsal spine; proved. Treated since 1944. Progressive collapse of thoracic spine and recurrent psoas abscess. Aspirations of psoas abscess; local streptomycin and P.A.S. Organism became resistant. T.B.3 was given from May 31 to August 7, 1951. Intermittent albuminuria and reducing substance in urine. Some anorexia. No anaemia.

Case 3.—A woman aged 64. Tuberculosis of right sacroiliac joint; proved. Treated by plaster bed, streptomycin and P.A.S., and operative fusion. Organism became resistant, and a course of T.B.3 was added from June 5 to September 21, 1951. Discontinued because of severe albuminuria, profound nausea, vomiting, and anaemia. Haemoglobin fell from 96% to 64%, necessitating blood transfusion. E.S.R. rose. Urine occasionally contained a reducing substance.

Case 4.—A woman aged 31. Tuberculosis of thoracolumbar spine; proved. Wound broke down after operative excision of the disease in spite of streptomycin and P.A.S. T.B.3 was given from June 5 to September 27, 1951; discontinued because of albuminuria and severe vomiting. No fall of E.S.R. or haemoglobin. A reducing substance was found in the urine.

Case 5.—A man aged 20. Tuberculosis of D.12 and L.1 and os calcis; proved. Wound broke down following excision of spinal lesion while on streptomycin and P.A.S. T.B.3 was given from June 26 to July 13, 1951, when heavy albuminuria led to its withdrawal.

Case 6.—A girl aged 16. Pott's paraplegia; proved. Failed to improve after plaster-bed and lateral rachotomy. T.B.3 added to streptomycin and P.A.S. from August 24 to September 17, 1951, when severe albuminuria and vomiting led to its discontinuation. E.S.R. and haemoglobin percentage unchanged. A reducing substance appeared in the urine.

Case 7.—A woman aged 69. Dorso-lumbar tuberculosis; proved. Lumbar abscess. Organism became resistant to

streptomycin and P.A.S. T.B.3 was given from September 6 to 25, 1951, when severe nausea and vomiting led to its discontinuation. Mild albuminuria. E.S.R. and haemoglobin unchanged. Reducing substance present in urine.

Case 8.—A woman aged 21. Tuberculosis of lumbar spine; proved. Wound broke down following excision of the disease. Course of T.B.3 was given from September 10 to 27, 1951, when albuminuria led to its discontinuation. Moderate nausea and anorexia throughout the course. E.S.R. and haemoglobin unchanged. Reducing substance was found in urine.

Discussion

No attempt has been made to assess the effect of T.B.3 on the tuberculous lesions in these cases. Since only eight patients were given the drug, and some for only a few weeks, any such deductions would be statistically invalid. We confine our remarks to the toxic effects of T.B.3.

None of this series remained free from toxic signs or symptoms while receiving the drug, and in all of them the drug was withdrawn because of this toxicity.

Albuminuria was found in every case at some time during the course, though its severity varied from case to case. Case 4 developed albuminuria while receiving only 50 mg. of T.B.3 a day, and this did not increase when the dose was raised to 200 mg. a day. In Case 5, on the other hand, very severe albuminuria occurred only when this full dose was reached, the course being immediately abandoned. We found no evidence of permanent renal damage following the courses of T.B.3, and albuminuria disappeared a few days after the drug was withdrawn in all cases. We feel, however, that the persistent albumin leak through the kidneys is evidence that the drug has a very definite toxic effect on this organ, and that long courses of the drug might well lead to irreversible changes.

In all but two of our cases a reducing substance appeared in the urine during the course. In Cases 4, 6, 7, and 8 this was a constant finding, while in Cases 2 and 3 it was intermittent. This substance was shown not to be a sugar, and was probably glycuronic acid, which appears in the urine during the detoxication of P.A.S. in the liver. All these cases were receiving P.A.S.

Only one case tolerated T.B.3 without developing anorexia, nausea, or vomiting to some degree. In Cases 1, 3, 4, 6, and 7 these disturbances were severe on a dose greater than 100 mg. a day, and led to a deterioration in the patient's general health. We were unable to reduce the severity of these symptoms by increasing the intake of glucose or by the administration of "avomine" or chlorbutol. We feel that such a disturbance of the general condition of a tuberculous patient can only do harm.

Case 3 showed a gradual fall of the haemoglobin level throughout the course of T.B.3 in spite of the administration of oral iron. The haemoglobin finally reached a level of 63% after nearly three months on the drug. This patient also experienced severe anorexia and vomiting from time to time during the course. No evidence of any haemolytic element could be found, and the anaemia was of the normocytic hypochromic type. After the course of T.B.3 a blood transfusion and the continued administration of iron soon led to cure of the anaemia.

Case 1 developed a similar type of anaemia but of slighter degree. In neither of these two patients was there any local sepsis at the disease site, and the sinus in Case 1 was at all times sterile. It seems probable that the digestive upsets led to deficient absorption of iron from the intestines. No fall of the white-cell count was seen in any of our patients.

The E.S.R. remained substantially unchanged in six cases and rose in two during the administration of T.B.3. We did not encounter the fall reported by other workers. No case developed any allergic manifestations while receiving the drug.

It is possible that our dosage was too high, but it is of interest that Case 2, an undersized boy of 9, tolerated the

full dosage of 200 mg. a day for several weeks a great deal better than most of the adult patients. In view of the work of Francis and Spinks, we felt that no useful therapeutic effects could be expected from a lower dosage.

Conclusions

The serious toxic effects of T.B.3 forced us to abandon this clinical trial in its early stages. Obviously we cannot draw any far-reaching conclusions from this limited experience. We feel, however, that the ill effects of the drug on the general condition of the patients are a very serious contraindication to its use in bone and joint tuberculosis.

The modern combination of a sanatorium regime with the administration of streptomycin and P.A.S. and a planned surgical attack on the disease is in our experience yielding good results. It is important also not to overemphasize the role of chemotherapy in a disease whose basic pathology is the avascular tubercle and caseation, for even the most active antituberculous drug may not reach the living organisms in the centre of the lesion.

The routine use of any fresh chemotherapeutic aids can be justified only if their therapeutic benefits outweigh any toxic effects. The general condition of the patient must not suffer during treatment, and there must be no permanent sequelae.

We believe that T.B.3 fails on the first of these conditions, and that its prolonged administration may lead to failure on the second also. In our opinion its use in bone and joint tuberculosis should be restricted to cases in which other methods are failing to arrest the disease, and in which the situation is becoming so critical that the risks must be accepted.

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At a meeting in Edinburgh on January 7 Dr. Charles Hill, Parliamentary Secretary to the Ministry of Food, discussed the possibilities of derationing some foods (*Scotsman*, January 8). Speaking of the shortage of butter, he said that it was not sufficiently realized that it took 20 pints of milk to make 1 lb. of butter, or that 60% more liquid milk was being consumed to-day than before the war. The drive for more meat had also affected production of butter, but it was hoped that Australia would be able considerably to increase supplies of butter to this country, though it would be unduly optimistic to expect a return to the large quantities of cheap butter which were available before the war. Dr. Hill said that there was enough oil and fat in the world to dispense with the rationing of margarine and cooking fat, but our difficulty was to be able to afford to buy the necessary supplies.