in the attack and before organic damage is done to the heart or kidneys. This view was expressed over two years ago by one of us (H. M.) as regards the heart when introducing Professor Philip S. Hench for the Honorary Degree conferred on him by the National University of Ireland.

Summary

Four cases of acute anuria treated with cortisone are reported. In two patients an allergic reaction in the kidneys was suspected, and both responded satisfactorily, making a rapid and complete recovery; in one the allergy was attributed to an overdose of sulphamerazine; in the other it was attributed to the sudden cessation of cortisone, which was being taken (100 mg. daily) for rheumatoid arthritis, and to the development of a sore throat, pyrexia, and rash; both factors preceded the anuria.

No definite conclusions can be drawn from the three apparently successful cases, as acute anuria is prone to develop a spontaneous remission.

We are indebted to Professor W. J. E. Jessop, of the Meath Hospital, Dr. Maurice Hickey, of the Mater Misericordiae Hospital, and Dr. Frank Geoghegan, of the National Maternity Hospital, Dublin, for carrying out the biochemical and pathological investigations. The tables were constructed by Mr. Ronan Kieran, of the Department of Anatomy, University College, Dublin.

REFERENCES

Bakken, K. (1947). *J. Path. Bact.*, **59**, 501.
Bergstrand, H. (1946). *Acta med. scand.*, **124**, 309.
Black-Shaffer, B. (1945). *Arch. Path.*, **39**, 301.
Bull, G. M., Joekes, A. M., and Lowe, K. G. (1949). *Lancet*, **2**, 229.
Moore, H., Jessop, W. J. E., O'Donovan, D. K., Barry, A. P., Quinn, B., and Drury, M. I. (1951). *British Medical Journal*, **1**, 841.
More, R. H., McMillan, G. C., and Duff, G. L. (1946). *Amer. J. Path.*, **22**, 703.
Selye, H. (1951). *Annual Report on Stress*. Montreal.
Thomas, L., and Good, R. A. (1951). *Proc. Soc. exp. Biol., N.Y.*, **76**, 604.

N,N'-DIBENZYLETHYLENEDIAMINE PENICILLIN: A NEW REPOSITORY FORM OF PENICILLIN

BY

A. P. FLETCHER, M.D., M.R.C.P.

AND

C. R. KNAPPETT, M.D., Dip.Bact.

(From the Department of Bacteriology and the Wright-Fleming Institute of Microbiology, St. Mary's Hospital Medical School, London, W.2)

Szabo, Edwards, and Bruce (1951), during a study of the properties of certain penicillin salts, discovered that the coupling of N,N'-dibenzylethylenediamine with penicillin resulted in the formation of a complex only very sparingly soluble in water. These authors described the properties of this complex, its preparation, and the fact that one molecule of base was coupled to two molecules of penicillin. A shortened name for this complex—benzethacil—will be used in this communication. Seifter *et al.* (1951), reporting on the toxicity of benzethacil to animals, found that this compound was approximately 25% more toxic than procaine penicillin to mice by intra-abdominal injection, but was not more toxic when given by intragastric drip, whilst its local analgesic action compared favourably with that of procaine hydrochloride. Elias, Price, and Merrion (1951) followed serum penicillin levels in man after the intramuscular injection of this compound, and concluded that it showed no significant toxicity and gave serum penicillin levels of greater duration than any reported with other forms of repository penicillin.

Benzethacil can be administered orally, and shows therapeutic activity by this route (Lepper *et al.*, 1952), but the present communication deals solely with the serum penicillin levels obtained after intramuscular injection.

Materials and Methods

Penicillin assay was performed by the *Sarcina lutea* plate technique (Food and Drugs Administration, Washington), using *Sarcina lutea* C.P.I.–1001. This technique, which uses penicillin dilutions made up in serum, allows adjustment for the influence of protein-bound penicillin, and is thus of considerable assistance in evaluating the significance of low penicillin levels.

With this technique reproducible zones of inhibition were obtained throughout the period of the experiment, as shown by the figures given in Table I. In practice a complete set of control plates was run with each set of serum assays. Serum penicillin levels were estimated from a line calculated from the individual control plates (see Ungar, 1951).

TABLE I.—*Diameters of Inhibitory Zones of Sarcina Plates*

Standard Penicillin in Serum (units/ml.)	Mean Diameter of Zone of Inhibition in mm.	Standard Deviation
0·10	23·9	±1·2
0·075	20·0	±0·96
0·05	18·8	±1·25
0·03	12·8	±1·45
0·02	9·1	±1·1

Benzethacil was supplied as an aqueous suspension in "tubex" ampoules containing 1 ml. (1 ml. contained 600,000 units of penicillin). The needle provided with the tubex syringe had a diameter of approximately 19 S.W.G.; the suspension could be injected without undue difficulty through this needle.

Nineteen volunteer male subjects took part in this investigation; their ages ranged from 19 to 33 years, and their weights from 10 to 15 st. (63.5 to 95.3 kg.). A single injection of 600,000 units of penicillin contained in one tubex ampoule was given into the gluteal muscles. Blood was withdrawn by venepuncture, and the serum, after being separated by centrifugation, was stored in stoppered bottles over solid CO_2 until used for assay.

Toxicity

Most of the subjects complained of aching at the site of injection for 24 to 48 hours. In no case was this severe. One subject developed a "serum sickness" reaction ten days after the injection. This reaction could not be positively attributed to the benzethacil since another possible antigen had been given shortly before. Despite the lack of positive evidence as to causation, this case is recorded, since benzethacil is excreted extremely slowly, and may give rise to unusual types of sensitivity response.

Results

The serum levels recorded are presented in Table II. It is seen that benzethacil administered by intramuscular injection gives sustained levels of serum penicillin considerably superior to any repository penicillin preparation yet developed. The findings in Table II support the view that even if benzethacil injections were spaced as far apart as 14 days a summation of dose effect might occur.

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	2	8	1	1				
0·02–0·029					1		7	7	9	7	6	8	3
<0·02. No detectable level							2	5	6	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 high, 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.

REFERENCES

Elias, W., Price, A. H., and Merrion, H. J. (1951). *Antibiot. and Chemother.*, **1**, 491.
Lepper, M. H., Rodriguez, J., Blatt, N., and Spies, H. W. (1952). Ibid., **2**, 171.
O'Brien, J. F., and Smith, C. A. (1952). *Amer. J. Syph.*, **36**, 519.
Seifter, J., Glassman, J. M., Begany, A. J., and Blumenthal, A. (1951). *Antibiot. and Chemother.*, **1**, 504.
Stollerman, G. H., and Rusoff, J. H. (1952). *J. Amer. med. Ass.*, **150**, 1571.
Szabo, J. L., Edwards, C. D., and Bruce, W. F. (1951). *Antibiot. and Chemother.*, **1**, 499.
Ungar, J. (1951). In *Recent Advances in Clinical Pathology, edited* by S. C. Dyke *et al.*, 2nd ed. Churchill, London.

CLINICAL TRIAL OF T.B.3 IN SURGICAL TUBERCULOSIS

BY

J. H. MAYER, T.D., M.B., F.R.C.S.
Orthopaedic Surgeon, Pembury Hospital, Kent

AND

P. GOWANS LAING, M.B., F.R.C.S.
Senior Surgical Registrar to the Bradford Group

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.