

This report, then, can be regarded as an interim account only, based on the examination of some 100 published papers on the subject. A further and more detailed investigation is in progress.

REFERENCE

Abercrombie, G. F. (1959). *J. Coll. gen. Pract.*, 2, 11.

DEAF OR DEAD?

A CASE OF SUBACUTE BACTERIAL ENDOCARDITIS
TREATED WITH PENICILLIN AND NEOMYCIN

BY

C. W. H. HAVARD, B.M., M.R.C.P.

LAWRENCE P. GARROD, M.D., F.R.C.P.

AND

PAMELA M. WATERWORTH, F.I.M.L.T.

From the Departments of Medicine and Pathology,
St. Bartholomew's Hospital, London

The following is the history of a patient who had to be warned that the treatment necessary to save his life would probably cause severe deafness. He accepted this consequence, and suffered it, but he is alive and well nearly a year later. The history also illustrates the value of tests of combined antibiotic bactericidal action in difficult cases of bacterial endocarditis.

Case Report

A police inspector aged 47 was admitted to St. Bartholomew's Hospital on February 8, 1958, complaining of not having felt well since December 4, 1957, when his urethral stricture (dating from 1946) had been dilated in this hospital. For several weeks past he had suffered from fever and night sweats, and for several days had noticed increasing lethargy and debility.

Physical examination revealed a well-built man (205 lb.—93 kg.) who was febrile (100° F.—37.8° C.) and obviously ill. There was no clinical cardiac enlargement, but examination of the heart showed evidence of a severe degree of aortic incompetence. The pulse frequency was 90 a minute and the pulse wave collapsing. The blood pressure was 130/50; a grade IV aortic diastolic murmur was conducted down the left border of the sternum, and the musical character of this murmur suggested rupture of an aortic cusp. A number of subungual splinter haemorrhages were visible, but there was no finger-clubbing and the spleen was not palpable. The urine contained no abnormal constituent, and microscopy of a centrifuged deposit revealed a few white and red blood cells only. The E.S.R. was 76 mm. in one hour (Westergren); the haemoglobin was 11 g./100 ml., the white blood count was normal, and the blood urea was 22 mg./100 ml. An E.C.G. and a chest x-ray examination were normal.

Bacteriological Findings.—A blood culture on the day of admission grew *Streptococcus faecalis*. This organism had a normal degree of sensitivity to penicillin (inhibition by 4 units/ml.) and to other antibiotics except tetracycline and streptomycin; the minimum inhibitory concentration of streptomycin was 50,000 µg./ml. (It was later verified that the *Str. faecalis* in his faeces was also highly resistant to streptomycin.) Tests of combined bactericidal action by the method of Martin, Sureau, and Chabbert (1952) showed that no combination of penicillin, streptomycin, tetracycline, chloramphenicol, erythromycin, novobiocin, vancomycin, or bacitracin, or any of these singly, completely sterilized the inoculum. A further experiment was done in which serial viable counts were made by an accurate method, using the more promising six antibiotics or combinations in a

concentration of 10 µg./ml. (penicillin 10 units/ml.), whether alone or in combination. The following were the mortalities after 24 hours: penicillin, 99.75%; erythromycin, 51%; vancomycin, 69%; penicillin + erythromycin, 60%; penicillin + vancomycin, 81%; Penicillin + streptomycin, 99.85%.

From this it appeared that penicillin alone was as effective as anything else, and treatment, which from February 10 had consisted of penicillin, 1 mega unit six-hourly, and streptomycin, 1 g. b.i.d., was continued from February 14 with penicillin only (2.5 mega units six-hourly) supplemented by probenecid, 0.5 g. q.d.s. This regime was continued for six weeks.

After four days the patient became and remained afebrile. His immediate progress was uneventful. The E.S.R. had fallen to 20 mm. in one hour by the end of the sixth week, and he not only felt restored to complete health but had gained 2.3 kg. in weight. The musical character of the aortic diastolic murmur had gradually disappeared, and the diagnosis of subacute bacterial endocarditis on a bicuspid aortic valve with rupture of one of the cusps seemed to be beyond dispute. No signs of relapse appeared over a further week of observation, and he was discharged from hospital on April 2.

Relapse

Two weeks after leaving hospital he complained of dysuria, and a few days later the night sweats and lethargy returned. On April 26 he was readmitted to hospital. He was febrile (101° F.—38.3° C.) and obviously ill, but the physical signs were essentially unchanged. The blood pressure was 130/50 mm. Hg and there was a definite though slight increase in the heart size. Microscopy of the urine revealed an excess of leucocytes and a few red blood cells; culture was sterile. The E.S.R. was 60 mm. in one hour, the haemoglobin was 8.9 g./100 ml., and the white blood count 7,200/c.mm., with a normal differential count. The blood urea was 23 mg./100 ml. and the urine concentration and dilution tests were normal.

Bacteriological Findings.—Blood cultures made on April 26 and 27 yielded a profuse growth of *Str. faecalis* (187 and 190 colonies per ml. in pour plates). This organism and that isolated originally were sent to Dr. S. D. Elliott, who kindly reported that they were identical, belonging to his type D 15, which is the type 9 of Sharpe and Shattock (1952). It was still inhibited by 4 units of penicillin per ml., but killed by penicillin much more slowly. The only remaining resource appeared to be neomycin. Although the organism grew in 10 µg. of this antibiotic per ml. (the minimum inhibitory concentration was 16 µg./ml.), either 5 or 10 µg. of neomycin per ml. combined with 10 units of penicillin per ml. proved to be completely bactericidal. This was the only combination found to sterilize the inoculum (of about 10⁸ streptococci per ml.) in all the tests made.

Treatment with penicillin, 2½ mega units six-hourly, streptomycin, 1 g. daily, and probenecid, 0.5 g. t.i.d. was started on April 28. By May 6 the full laboratory findings were available, and intramuscular neomycin, 0.5 g. eight-hourly, replaced the streptomycin and probenecid, the patient's consent having been obtained for the use of a drug which would probably make him deaf. He became and remained afebrile after five days' treatment.

Assays of the antibiotics in four specimens of blood on May 7 and 8 showed a penicillin content varying from 23 to 5 units/ml. and of neomycin from 32 to 8 µg./ml. according to the interval since the last dose.

After 10 days' treatment with neomycin granular casts were noticed on microscopy of the urine, and after two weeks albumin was detected on routine testing. By the end of 34 days the blood urea had risen to 63 mg./100 ml. However, this was transient, and within one month of discontinuing the neomycin the blood urea had fallen to 40 mg./100 ml. and there were no casts on microscopy of the urine.

The first symptoms of deafness appeared on the 28th day of neomycin treatment: these symptoms became more severe. Neomycin therapy was discontinued on the 35th day. Nevertheless the deafness progressed, and by August 8 (60 days after the beginning of neomycin therapy) audiograms revealed a total loss of cochlear function.

Neomycin was discontinued on June 9. The patient was discharged from hospital two weeks later and has remained well. His deafness is complete, but there are no symptoms referable to the cardiovascular system, and the heart size has remained unchanged over the last six months.

Discussion

It is generally accepted that bactericidal antibiotics are needed for the treatment of subacute bacterial endocarditis. In this case the bactericidally synergic combination of penicillin and streptomycin, which is usually successful in the treatment of *Str. faecalis* endocarditis (Hunter, 1946; Cates, Christie, and Garrod, 1951; Robbins and Tompsett, 1951), was inapplicable owing to the high degree of resistance of the organism to streptomycin. The less complete bactericidal action of penicillin proved inadequate. The alternative combination of penicillin and neomycin proved to be completely bactericidal, and the clinical result justified the confidence placed in it. It is possible that a shorter course might have effected a cure, with less or no damage to hearing, but when a patient has relapsed after one long and apparently successful course, there is natural reluctance to curtail another.

A minor feature of interest in this case is the origin of the infection. *Str. faecalis* endocarditis occurs in young women as a complication of septic abortion and in older men as a consequence of infection of the urinary tract. In this patient, dilatation of a urethral stricture precipitated it, as in Case 1 of the series described by Robbins and Tompsett (1951). This is evidently a hazardous procedure in men with heart valves predisposed to infection, and, should it have to be repeated in our patient, protection with a bactericidal antibiotic, possibly vancomycin in preference to further neomycin, will have to be provided.

Summary

Infection of the aortic valve following dilatation of a urethral stricture in a man aged 47 was caused by a strain of *Str. faecalis* highly resistant to streptomycin, although of normal sensitivity to other antibiotics except tetracycline. A long course of penicillin in large doses was followed by relapse.

Only a mixture of penicillin with neomycin was found to be completely bactericidal for this organism. These antibiotics were accordingly given, and the patient was alive and well seven months later, but totally deaf.

We are indebted to Dr. A. W. Spence, under whose care the patient was treated, for permission to publish this case.

REFERENCES

- Cates, J. E., Christie, R. V., and Garrod, L. P. (1951). *Brit. med. J.*, **1**, 653.
 Hunter, T. H. (1946). *Amer. J. Med.*, **1**, 83.
 Martin, R., Sureau, B., and Chabbert, Y. (1952). *Bull. Soc. méd. Hôp. Paris*, **68**, 1192.
 Robbins, W. C., and Tompsett, R. (1951). *Amer. J. Med.*, **10**, 278.
 Sharpe, M. Elisabeth, and Shattock, P. M. Frances (1952). *J. gen. Microbiol.*, **6**, 150.

RECURRENT PHLYCTENULAR KERATO- CONJUNCTIVITIS TREATED BY DESENSITIZATION TO TUBERCULIN

BY

ARNOLD PINES, M.D., M.R.C.P.Ed.

Department of Tuberculosis and Diseases of the
Respiratory System, Edinburgh University

Though usually a benign and transient phenomenon, phlyctenular conjunctivitis can be distressing and disabling, particularly when the cornea is involved. In mild cases local treatment may suffice, but it often fails when there are more severe manifestations. Since phlyctenules are allergic phenomena, most often to tuberculo-protein, the antituberculous drugs have often been given in treatment with apparent success. In the case described below they had no effect, and more fundamental treatment had to be undertaken.

Case Report

A boy aged 11 was seen in March, 1957. Since the age of 6 he had had four or five attacks of phlyctenular kerato-conjunctivitis a year. These attacks had been distressing and he had lost several months of attendance at school each year. Treatment had always been on general lines, and he had never been given antituberculous chemotherapy. Both eyes had been equally affected, and small scars had remained in each cornea at the centre and at the limbus, though these had not affected vision. In the most recent attack a phlyctenule had appeared in each eye, and there were moderate blepharospasm and photophobia and also some general disturbance. No lesions of the retina or choroid were present. A radiograph of the chest showed a very large calcified paratracheal gland and two small calcified lesions in the right upper lobe; a radiograph taken in 1952 had shown identical changes. A Mantoux test in 1955 had been positive to 0.1 T.U. (1:100,000); this was repeated in 1957 in the same dilution, and was again positive, the induration measuring 10 by 8 mm.

The presence of these calcified tuberculous pulmonary lesions and the marked sensitivity to tuberculin indicated that the phlyctenular kerato-conjunctivitis was an allergic response to tuberculo-protein. The patient was admitted to hospital for a trial of chemotherapy and was given *para*-aminosalicylic acid (P.A.S.), 5 g., and isoniazid, 100 mg., twice daily from March 21. Cortisone eyedrops were given daily. Both phlyctenules gradually subsided, but after five weeks the right phlyctenule reappeared, accompanied by blepharospasm and photophobia, though chemotherapy was still being given.

Tuberculo-protein is present in the bodies even of dead bacilli, and therefore it was thought that further chemotherapy by itself might well be ineffective. It was rational to abolish the allergic state by desensitization to the offending allergen, tuberculo-protein. The phlyctenules had recurred so often over five years and the patient's life had been disturbed so much that it was reasonable to attempt the rather prolonged treatment needed.

In severe allergic states desensitization may be greatly eased and speeded by a cover of corticosteroids (Pines, 1957). The patient was therefore given prednisolone, 5 mg. three times daily, while P.A.S. and isoniazid were continued to guard against the very remote possibility of reactivation of the pulmonary tuberculosis. 0.1 ml. of old tuberculin, 1:100,000 dilution, was given intramuscularly without reaction; afterwards the dose was approximately doubled daily without incident. On the twelfth day he had a slight headache, fever, and vomiting with 1 ml. of old tuberculin, 1:1,000. The prednisolone was increased to 5 mg. four times daily and desensitization was continued. A mild reaction followed the injection of 0.75 ml. of old tuberculin