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PENICILLIN-RESISTANT SUBACUTE BACTERIAL ENDOCARDITIS TREATED BY A COMBINATION OF PENICILLIN AND STREPTOMYCIN

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In subacute bacterial endocarditis the choice of treatment depends upon the sensitivity of the infecting organism to antibiotics. Fortunately most of these organisms are sensitive to penicillin, when two million units of penicillin daily for four to six weeks can be expected to eliminate infection. In about 1% of cases, however, the infecting organism is highly resistant to penicillin, growth being uninhibited by less than 1 unit of penicillin per ml.; and then enormous amounts of penicillin may fail to eradicate the disease. As these cases are rare the best methods of treatment cannot be decided by adequate clinical trials and can be deduced only from reports on small groups or even single cases. In the past year we have treated four patients in whom the infecting organisms were resistant to penicillin, growth being inhibited by 4, 3, 4, and 4 units of penicillin per ml. respectively. Various courses of antibiotics were given, and of these the combined use of penicillin and streptomycin seemed to be the best. This form of treatment was first advocated by Hunter (1947) and has since been proved of value by Robbins and Tompsett (1949), but it has not yet been reported in this country. Laboratory studies with the infecting organisms in two of our cases have shown that the bactericidal action of penicillin was enhanced by the addition of streptomycin but was partially inhibited by the addition of "aureomycin."

Case 1

A married woman aged 36 was transferred to this hospital in January, 1950. Seven months previously, when four months pregnant, she aborted: this was followed by femoral thrombosis and an empyema from which was grown *Staphylococcus aureus*. The patient was given penicillin and became convalescent. Two months before admission she had a cerebral embolism, and blood culture grew a "micrococcus resistant to penicillin and sensitive to streptomycin." Streptomycin, 2 g. daily, did not control the infection, and the organism became resistant to streptomycin.

On admission the patient was wasted and was in early heart failure. She had signs of mitral-valve disease with subacute bacterial endocarditis, and there was a left-sided hemiplegia. Blood culture yielded *Streptococcus faecalis*, the growth of which was inhibited by 4 units of penicillin, 30 µg. of streptomycin, 20 µg. of chloramphenicol, and 0.15 µg. of aureomycin per ml.

Aureomycin, 2 g. daily, was given for six weeks. During this time fever was reduced from 101 to 99° F. (38.3 to

37.2° C.): blood culture was positive on the third and sixth days, and became negative thereafter. However, six days after the end of this course of treatment fever rose to 101° F. and blood culture was again positive. Sensitivity of the organism to aureomycin had not changed.

Aureomycin, 2 g., and 20 million units of penicillin were then given daily. Once more the fever fell to about 99° F., but the patient lost her appetite and vomited, became weak, listless, and mentally confused. Aureomycin was therefore stopped after 15 days; penicillin alone was given for the next two days. Blood culture taken at that time was negative. Streptomycin, 4 g., was then given with the daily dose of 20 million units of penicillin, and this combined treatment was continued for six weeks. The patient's appetite returned and she improved mentally, but her muscle at the sites of injection became indurated and painful, and heart failure slowly increased. After this course of treatment she was afebrile except for one spike of 99.4° F. (37.4° C.). Blood cultures were negative. She died from heart failure 17 days after treatment ended, and culture of the heart valves grew contaminants only: organisms were seen in sections of the vegetations, but most of them stained badly and were pleomorphic.

Comment. — Although the growth of infecting organisms was inhibited by 0.15 µg. of aureomycin per ml., infection returned after a six-weeks course of 2 g. a day. The infection was apparently controlled while aureomycin and penicillin were given together, but aureomycin had to be stopped because the patient became intolerant of it. Streptomycin and penicillin given together likewise apparently controlled the infection, and infection did not return in the 17 days that the patient survived.

Case 2

A man aged 57 was transferred to this hospital in March, 1950. Nine months previously subacute bacterial endocarditis had been diagnosed; the infecting organism was *Str. faecalis*, and its sensitivity to antibiotics was similar to that found later. The following courses of treatment failed to eliminate infection: 1.8 million units of penicillin daily for one month; 2 g. of streptomycin daily for two weeks, increased to 3 g. daily for one week; 0.5 g. of aureomycin for one day, 2 g. daily for a week, 4 g. daily for 13 days, increased finally to 8 g. daily for one month. (Each increase in dosage was made because low-grade fever appeared.)

On admission the patient was fibrillating; he had aortic-valve disease with signs of subacute bacterial endocarditis. There was no heart failure and he was not wasted.

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Blood culture yielded *Str. faecalis*, the sensitivity of which to antibiotics was as follows:

	Minimum Inhibitory Concentration (per ml.)	Maximum Concentration Allowing Growth (per ml.)
Penicillin	3 units	2 units
Streptomycin	30 µg.	10 µg.
Chloramphenicol	6 µg.	3 µg.
Aureomycin	0.1 µg.	0.05 µg.

Twenty million units of penicillin, 24 g. of "caronamide," and 2 g. of aureomycin were given daily. His temperature fell from 100° to 97° F. (37.8 to 36.1° C.) within 24 hours, but rose again between the eighth and twelfth days to 102° F. (38.9° C.). Aureomycin was therefore stopped and penicillin with caronamide was continued for two days. Fever persisted, but blood culture taken at that time was negative. Streptomycin, 4 g., was then given with the penicillin and caronamide, and this combined treatment was continued for seven weeks. His temperature fell to normal in five days, and blood cultures remained negative. The patient was alive and free from infection six months later, though vestibular damage interfered with his walking and he had early heart failure.

Comment.—Although the infecting organism was sensitive to 0.1 µg. of aureomycin per ml., infection returned after a seven-weeks course, including 8 g. daily for one month. When aureomycin and penicillin were given together fever was not controlled. After a combined course of penicillin and streptomycin, infection has apparently been controlled.

Case 3

A man aged 41 was admitted into this hospital in October, 1950. In January, 1946, he had had subacute bacterial endocarditis with a right-sided hemiplegia. The underlying lesion was rheumatic heart disease affecting both the aortic and the mitral valves. The infecting organism was a *Str. viridans* three times more sensitive to penicillin than the Oxford H staphylococcus. The patient was given 500,000 units of penicillin daily for a month, and recovered. In October, 1946, three infected teeth were removed under an umbrella of 500,000 units of penicillin daily for five days without untoward effect. In January, 1949, six more teeth were removed under an umbrella of 600,000 units of procaine penicillin daily for three days, again without untoward effect. In August, 1950, he was once more admitted for dental extraction; there was some gingivitis, but no evidence of bacterial endocarditis, and he had no fever and the E.S.R. was 6 mm. in one hour. Penicillin, 500,000 units, was given every six hours from 7 p.m. on August 29 to September 4. Five teeth were extracted on August 31 and five more on September 2. The gums healed naturally, and the patient was discharged on September 6 with no fever and an E.S.R. of 11 mm. in one hour.

At a follow-up five weeks later he was found to have signs of subacute bacterial endocarditis. He had become thinner; although he was afebrile, his E.S.R. was 42 mm. in one hour, and blood culture grew *Str. viridans*. The organism was highly resistant to penicillin, growing in 2 units but being inhibited by 4 units of penicillin per ml. It was almost completely inhibited by 3 µg. of streptomycin per ml.

The patient was admitted at once and was given 2 million units of penicillin daily while the resistance of the organism was being measured. Blood culture taken during this time was found to be positive. He was then given 4 g. of streptomycin and 20 million units of penicillin daily for six weeks. During this course his temperature rose to 100° F. (37.8° C.) and his E.S.R. remained raised, between 22 and 38 mm. in one hour. He developed a slight lumbar pad of oedema but no other evidence of heart failure, and this oedema was in part due to the repeated intramuscular injections. At the end of treatment the function of both labyrinths was

destroyed. The patient was alive and free from infection three months after the end of treatment.

Comment.—A second attack of bacterial endocarditis followed dental extraction in spite of an umbrella of 2 million units of penicillin daily for six days. The organism, a *Str. viridans*, was highly resistant to penicillin but relatively sensitive to streptomycin. The patient was apparently cured by 20 million units of penicillin and 4 g. of streptomycin daily for six weeks.

Case 4

A man aged 63 was transferred to this hospital in January, 1951. Five years previously, in 1945, he developed subacute bacterial endocarditis, and *Str. viridans* was isolated from the blood. Penicillin, 500,000 units a day for four weeks, apparently eliminated the infection and he remained well until July, 1950, when after prostatectomy he became febrile and *Str. faecalis* was found in blood culture. He was given penicillin and streptomycin for about three weeks; details of this course of treatment are not available, but the daily dose was probably small. A week later blood culture was again found to be positive. He then received a long course of penicillin and streptomycin: an average daily dose of 16 million units of penicillin was given for six weeks, and during the first 19 days he also received an average daily dose of 2.5 g. of streptomycin. During the last three weeks of this course the patient was afebrile, but fever then returned and blood culture again became positive. The patient was then given chloramphenicol for 10 weeks, with an average daily dose of 3.8 g.; even when the daily dose was as high as 7 g. a day he remained febrile and the blood culture positive. Three days after the end of the last course he was admitted to this hospital.

On admission the patient had a rough systolic mitral murmur with signs of subacute bacterial endocarditis. He was not wasted and there was no evidence of heart failure.

Blood culture yielded *Str. faecalis*, and its sensitivity to antibiotics was as follows:

	Minimum Inhibitory Concentration (per ml.)	Maximum Concentration Allowing Growth (per ml.)
Penicillin	4 units	2 units
Streptomycin	125 µg.	62.5 µg.
Chloramphenicol	2.5 µg.	1.25 µg.
Aureomycin	0.15 µg.	0.07 µg.

Five days after admission the patient developed a severe anterior myocardial infarction. Three days later 20 million units of penicillin and 4 g. of streptomycin were given daily; the serum levels were 128 units of penicillin and 64 µg. of streptomycin per ml. The temperature promptly fell to normal and remained there, and blood culture was sterile. But the patient rapidly developed heart failure, from which he died five days after treatment began. At necropsy there were large vegetations on the mitral valve and extensive myocardial infarction due to a septic embolus in the left coronary artery. Cultures from the vegetations and from the myocardial infarct yielded *Str. faecalis*.

Comment.—A second attack of subacute bacterial endocarditis followed prostatectomy. Infection returned after two combined courses of penicillin and streptomycin; but the dosages were smaller than those used in the other three cases. Chloramphenicol failed to control the infection. The organism was highly resistant to streptomycin, and, although a third combined course of penicillin and streptomycin promptly controlled the fever, the patient died from heart failure after five days. An organism similar to that causing the original infection was cultivated at necropsy.

Laboratory Observations

The strains of streptococcus from Cases 1, 2, and 4 were typical enterococci (*Str. faecalis*). They were oval cocci forming only short chains; they fermented

mannite, resisted heating to 60° C., and reacted with Lancefield's Group D serum. That from Case 3 had none of these characters and is classified as *Str. viridans*.

The sensitivities of these organisms to single antibiotics have been mentioned. Studies were also made of the action of pairs of antibiotics on some of them. The streptococcus from Case 1 was highly sensitive to aureomycin, and it seemed promising to combine this drug with penicillin. When both were added to broth in concentrations round about their lower individual limit of efficacy for inhibiting growth there was a slight additive effect. When, on the other hand, such cultures were not merely observed for presence or absence of growth after one to two days, but were subjected to viable counts at intervals of 2, 4, 6, 8, and 24 hours, a different picture was obtained. Penicillin alone (50 units/ml.) produced a steady fall in the number of survivors; aureomycin alone (5 µg./ml.) kept the population stationary: the two together had a merely intermediate effect, the death rate being slower than that produced by penicillin only. Similar results were obtained later with the streptococcus from Case 4, using penicillin (10 units/ml.) and aureomycin (5 µg./ml.). They were also obtained with a more sensitive organism, the Oxford H staphylococcus; penicillin, 0.1 unit/ml., caused a 99.99% mortality in eight hours; aureomycin, 0.3 µg./ml., kept the count almost constant: the two together caused a mortality of only 96%.

It was thus evident that, whatever the ultimate fate of the organisms, aureomycin reduced the rate at which they were killed by penicillin. On the other hand, streptomycin, which is itself bactericidal and not merely bacteriostatic, increased it. In an experiment with the streptococcus from Case 1, penicillin, 10 units/ml., caused a mortality of about 99.99% in eight hours; streptomycin, 10 µg./ml., had the same effect in four hours: the two drugs together reduced survivors to this level in between two and three hours. Even in a concentration itself sub-inhibitory, streptomycin accelerated the action of penicillin. This was shown with the streptococcus from Case 4: this organism was not inhibited by 50 µg. of streptomycin per ml. and slow growth occurred in this concentration. When it was added to medium also containing 10 units of penicillin per ml., the number of survivors at each time interval was smaller than in medium containing this amount of penicillin alone, the difference varying from about four-fold at four hours to thirtyfold at 24 hours.

These results correspond with those recently reported for combinations of antibiotics by Jawetz and his colleagues which are discussed below. In view of the thorough and decisive nature of their observations it seems unnecessary to describe our own in detail, or to pursue them further than they were carried at the time to give guidance for the treatment of individual patients.

Discussion

When the infecting organism is sensitive to penicillin the best form of treatment is penicillin alone. When the infecting organism is resistant to penicillin large amounts of penicillin may succeed, either when given alone (Hunter, 1946) or when given with some substance that delays penicillin excretion (such as caronamide) (Loewe, Rosenblatt, and Altire-Werber, 1946; Grossman, Feldman, Katz, and Brams, 1947; Hagedorn and Scheifley, 1948; Leaman, Wikingsson, Webster, and Shaw, 1949; Stuart-Harris, Colquhoun, and Brown,

1949); and therefore, although failures have also been reported (Zeller, Hirsh, Dowling, Hussey, and Robinson, 1948; Cates, 1949), it is possible that the success of penicillin combined with streptomycin in Cases 1, 2, and 3 might have been achieved by the same amounts of penicillin alone.

Streptomycin will sometimes succeed in penicillin-resistant infections (Priest and McGee, 1946; Paul, Bland, and White, 1947; Massell, Zeller, Dow, and Harting, 1948; Pearsall, Pillow, and Wood, 1948; Naegele, 1949), but in only 4 of the 18 cases analysed by Hunter could streptomycin be said clearly to have cured the patient. The resistance of the infecting organisms to streptomycin is of great importance, and of the 18 cases reviewed by Hunter (1947) "treatment was not successful in any case in which the organism required more than 8 µg. per ml. for *in vitro* inhibition of growth"; Naegele, however, reported one success with an organism that needed 16 µg. per ml. to inhibit its growth. In our Cases 1 and 2 not only were the infecting organisms relatively resistant to streptomycin, needing 30 µg. per ml. to inhibit growth, but also in each a course of streptomycin failed to eliminate infection; therefore the apparent control of infection that was achieved by a combined course of penicillin and streptomycin can hardly be attributed solely to the streptomycin in that course.

More recently aureomycin has been tried in penicillin-resistant infections, including *Str. faecalis*, micro-aerophilic streptococci, and penicillin-resistant *Str. viridans*; but results have been disappointing, for of 10 patients reported by various authorities (Brainerd, Lennette, Meiklejohn, Bruyn, and Clark, 1949; Harvey, Mirick, and Schaub, 1949; Dowling, Lepper, Caldwell, Whelton, and Sweet, 1949; Schoenbach, 1949) aureomycin failed to cure infection in six, and clearly succeeded in only two. Likewise, in Cases 1 and 2 infection returned after treatment with aureomycin, although the organisms in both were sensitive to this antibiotic.

In 1946 Hunter reported an infecting organism which was resistant to penicillin and streptomycin separately but sensitive to the combination of these two drugs; the patient was cured by a daily dose of 4 million units of penicillin and 4 g. of streptomycin. In 1947 he advised that the combination should be used if the infecting organism showed some sensitivity to both antibiotics, and the success of this treatment has been confirmed by his own experience since then (Hunter, 1950, personal communication), although his penicillin dosage has been increased to about 10 million units daily. Robins and Tompsett (1949) gave a daily dose of 6 million units of penicillin and 2 g. of streptomycin (or dihydrostreptomycin) to six patients with enterococcal bacteraemia (five with subacute bacterial endocarditis); four patients were apparently cured and the other two died during treatment. They made *in vitro* studies of the combined effect of these antibiotics, and reported that the effect of mixing the two was at least that of summation; however, they studied the bacteriostatic and not the bactericidal effect of combining the two drugs.

Robbins and Tompsett (1951) have subsequently described in detail a total of eight cases of penicillin-resistant streptococcal endocarditis (including those previously referred to). Their experience, more extensive than our own, tallies closely with it. It seems that

enterococcal endocarditis is apt to occur in elderly men, often as the result of lesions of the urinary tract, or in younger women, in whom a common source of infection is the uterus. Penicillin was demonstrably ineffective in controlling these infections, as was aureomycin in one case. On the other hand, combined treatment with penicillin and streptomycin succeeded in eliminating the infection in every case in which a full course was given, and five patients made a complete recovery, including one infected with a streptococcus having the penicillin-resistance of an enterococcus but not its other characters. Their three fatal cases had highly unfavourable features, and death occurred early during treatment in two of them.

The laboratory findings reported here indicate that the bactericidal effect of combining penicillin and streptomycin is more than additive, and thus afford a rational explanation for the success of treatment with this combination of drugs. It has similarly been shown that aureomycin impairs the bactericidal action of penicillin, at least over a limited period of time. We owe the conception of these experiments to the paper by Jawetz, Gunnison, and Coleman (1950), which became available to us while Case 1 was under treatment: in this they showed that penicillin and streptomycin act synergically on enterococci, but chloramphenicol reduces the bactericidal activity of penicillin. It seems likely that aureomycin would behave similarly, and this we found to be so.

Jawetz and his colleagues have since extended their original observations: Jawetz and Gunnison (1950) analyse the reactions of enterococci and viridans streptococci to penicillin and streptomycin; Jawetz and Speck (1950) report that chloramphenicol interferes with the curative action of penicillin on *Str. pyogenes* infection in mice; more recently Gunnison, Coleman, and Jawetz (1950a, 1950b) have further examined the effect of combinations of antibiotics on enterococci and other organisms, and shown that both aureomycin and terramycin behave like chloramphenicol in reducing the rate of killing by penicillin. The full clinical significance of this work remains to be assessed, but it seems possible, as suggested in the *British Medical Journal* (1950), that any combination of a bacteriostatic with a bactericidal antibiotic of the penicillin type may prove inefficient, because the latter can act only on multiplying bacteria.

The development of subacute bacterial endocarditis after dental extraction is not always prevented by prophylactic penicillin, and there are at least five failures in the literature (Glaser, Dankner, Mathes, and Harford, 1948). Case 3 is of particular interest for two reasons. First, the dose of 2 million units daily for six days is so far the largest dose that has failed to prevent bacterial endocarditis. Secondly, Perrin Long (1950, personal communication) observed that it was unwise to give penicillin for an appreciable time before dental extraction, because the bacterial flora of the mouth rapidly became penicillin-resistant; the danger of this is supported by our experience, because the patient's teeth were removed in two sittings, the second on the fourth day of the prophylactic course. Although it seems likely that in this case prophylactic penicillin actually induced an endocarditis more formidable than that against which it was expected to guard, it is only fair to observe that there was no comparable case in the whole M.R.C. series of 442 patients (Cates and Christie, 1950), many of whom had dental extraction at the end of long courses of penicillin.

Summary

Four patients are reported with subacute bacterial endocarditis due to penicillin-resistant organisms, three being enterococci.

Courses of streptomycin and of aureomycin were given to two and a course of chloramphenicol was given to a third, all without success. The combination of penicillin and aureomycin failed to control the fever in one and produced toxic symptoms in another.

In three the infection was apparently controlled by a combination of 20 million units of penicillin and 4 g. of streptomycin daily for at least six weeks. One of these patients died later from heart failure; the other two are alive and well, apart from vestibular damage. The fourth patient died from heart failure on the fifth day of treatment, and although clinical response was prompt necropsy indicated that infection had not been eliminated; previously this patient had relapsed after smaller dosages of penicillin and streptomycin given together. The infecting organism was highly resistant to streptomycin.

In vitro, the bactericidal action of penicillin on the two organisms so tested was accelerated by the addition of streptomycin and retarded by the addition of aureomycin.

In one patient tooth extraction during the prophylactic use of 2 million units of penicillin daily for six days was followed by subacute bacterial endocarditis due to a penicillin-resistant organism.

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