THE NEW PENICILLINS IN ENDOCARDITIS*

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FEW infections can kill a human being as rapidly as acute staphylococcal endocarditis in its most fulminant form. Infections caused by penicillinase producing staphylococci have been particularly difficult to manage. Successful treatment has been accomplished by combinations of antibiotics, by vancomycin, and even by huge doses of penicillin G. Still, the problem of therapy remains formidable. Since 1960, when methicillin first became available to clinicians, a number of patients have been treated with this antibiotic. Subsequently, oxacillin, nafcillin and perhaps others have been employed with promising results. In addition, a few cases of streptococcal endocarditis have been treated with these drugs. It is my purpose to review some cases collected from the literature, to describe one of our own cases, and to give a progress report on some experiments with two penicillinase resistant penicillins in treatment of experimental staphylococcal endocarditis in dogs.

Clinical Observations

In man, the ultimate outcome is likely to be influenced by the interplay of a number of factors, both clinical and chemotherapeutic. The most important clinical factors include the duration of infection, the age of the patient, the valve involved, and the distribution of metastatic staphylococcal lesions. Chemotherapeutic factors include the daily dose of drug, the duration of treatment, peak blood levels or antistaphylococcal titres achieved, constancy of maintenance of antistaphylococcal titres, minimal inhibitory and bactericidal concentrations of the antibiotic *in vitro*, degree of resistance to β -lactamase, and degree of binding of antibiotic by serum.

*The experimental work reported in this presentation will be published separately as a full scale manuscript. It was performed in collaboration with John C. Garancis, M.D., Janet S. Beasley, B.A., and Nancy Scott, B.S.

In analyzing reported cases of staphylococcal endocarditis, chiefly in the American literature, I have restricted our attention to 29 cases where success or failure could be attributed specifically to a penicillinase resistant penicillin (Bunn, 1960; Campeau *et al.*, 1961; Douthwaite *et al.*, 1961; Allen *et al.*, 1962; Sabath *et al.*, 1962; Simon and Rantzi, 1962; Doyle, 1964; and Quinn, 1964). The duration of treatment seems to be more important than the daily dosage. The infection was eradicated in 21 of 23 cases treated for 15 days or more. Six patients died during the first 14 days of treatment despite daily doses of methicillin or oxacillin varying from 6 to 12 grams.

One of our most gratifying cases was that of a 24-year-old woman admitted to the hospital desperately ill with staphylococcal endocarditis, meningitis, pyarthrosis and purulent splenitis. Her course is depicted in Fig. 1. The points I wish to emphasize in this case are first that her clinical improvement preceded a drop in temperature, second that positive blood cultures were encountered six days after the beginning of ultimately successful treatment, and third, that high antistaphylococcal titres were maintained throughout the course of her treatment.

Experimental Model

Our experimental model of endocarditis in dogs is prepared by surgical perforation of the aortic cusp, followed in three weeks by the intravenous inoculation of a penicillinase producing staphylococcus (Walker and Hamburger, 1959). We have employed two strains, one a group III and the other an 80/81, both originally recovered from human cases of endocarditis. Untreated dogs become ill in two to five days and succumb in seven to 12 days. A few colonies of staphylococci appear early in the blood cultures. The colony count then rises to the 100's and finally, a day or two before death, to the 1,000's.

Gross vegetations are sometimes but not always seen on the heart valves. Fig. 2 shows one of the largest we have encountered. Micro-

FIG. 3.—Microscopic section of aortic vegetation, showing huge mass of staphylococci embedded in fibrin $\times 970$.

scopically, however, acute endocarditis is always present, easily recognised in the sections of the aortic, and often of the mitral valve. In an early lesion, shown in Fig. 3, great masses of staphylococci are exhibited in fibrin. Myocarditis is extremely common (Fig. 4). Typical lesions appear regularly in the kidneys (Fig. 5). Fig. 6 shows the suture line which repairs the incision in the aorta through which the valve is perforated.

All autopsies are performed under aseptic conditions. The control dogs are sacrificed when it is evident they cannot survive another 24 hours. Weighed aliquots of tissues are ground and cultured quantitatively. Four representative colonies from each positive culture are phage typed and tested for sensitivity to penicillin G. Cultures in more than 50 untreated dogs show remarkable constancy in the numbers of staphylococci which colonize various organs. Fig. 7 shows the numbers recovered from a typical

control dog. Most important is the demonstration of the concentration in valvular vegetations of 10^8 to 10^{11} , i.e., 100 to 100,000,000 times as many as are found elsewhere.

Two years ago we undertook a series of therapeutic experiments. Because the muscle mass of a dog is insufficient to permit of multiple daily injections for several weeks, we elected to treat the dogs with compounds which are absorbed from the gastrointestinal tract. We treated the first five dogs with biphenyl penicillin, and the next 16 with oxacillin. Because of the importance of delivering drug to the lesions as constantly as possible, we hired medical students to treat the animals at 8.00 p.m. and midnight, in addition to three evenly spaced treatments given by the day staff.

Dogs have been treated for one week, three weeks and four to five weeks. Records have been kept of their daily temperature, blood

FIG. 4.—Myocarditis in experimental canine staphylococcal endocarditis.

FIG. 5.—Kidney in acute experimental canine staphylococcal endocarditis.

FIG. 6.—Suture line in aorta through which perforation of aortic cusp was performed in experimental canine staphylococcal endocarditis.

FIG. 7.—Staphylococci per gram of tissue in experimental canine staphylococcal endocarditis. (Reproduced from 'Antimicrobial Agents and Chemotherapy, (1963) (Hamburger, p. 708), with permission of the American Society for Microbiology.)

FIG. 8.—Mitral vegetation in cured experimental canine staphylococcal endocarditis.

FIG. 9.—Bacteriological failures after four weeks treatment with oxacillin.

cultures, serum antibiotic levels and serum antistaphylococcal titres. Since dogs absorb oxacillin poorly, large doses in terms of milligrams per kilogram have been necessary.

Four of seven dogs treated with oxacillin four or five weeks were cured, clinically, bacteriologically and histologically. Only two of six dogs treated three weeks have been cured, but none of the three treated one week. Fig. 8 is a photograph of a vegetation in a cured dog. Cultures and histologic sections of these lesions were free of staphylococci.

Fig. 9 shows cultures of the tissues at autopsy of three dogs which were clinically well during and after treatment but where the staphylococcal infection was not eradicated. The individual organs cultured are arranged along the bottom of the figure.

The first dog (63-194) was clinically well nine days after cessation of treatment when he died suddenly of rupture of the suture line in the aorta. All his tissues, including both aortic and mitral valves, contained large numbers of staphylococci. The second dog (63-423) failed to clear its blood stream during treatment, though it appeared clinically well. Believing that the staphylococci recovered from the blood were probably shed from an infected suture line, we persuaded our surgeon to explore the aorta in order to replace the infected portion

FIG. 10.—Peak antistaphylococcal titres in dogs with experimental staphylococcal endocarditis treated with oxacillin.

FIG. 11.—Oxacillin treated experimental staphylococcal endocarditis. Relation of outcome to percentage of antistaphylococcal serum titres of 1:2 or greater.

with a prosthesis*. The dog died on the operating table. To our surprise, the suture line and heart valves were sterile, but staphylococci were recovered from the kidney, liver, spleen and myocardium. The third dog (63-426) seemed clinically cured and displayed negative blood cultures four weeks after cessation of treatment. However, at autopsy the suture line remained heavily infected though the remaining tissues were sterile or virtually so. This dog would undoubtedly have succumbed eventually.

It seemed desirable to look into the relation of the animals' antistaphylococcal titre to cure or failure. Two parameters were analysed: the peak titre at any time during the dog's treatment, and the percentage of all titres measured during treatment which were 1:2, 1:4 or higher. Fig. 10 shows the peak titre for each dog. The solid circles represent cured dogs, the open circles failures. It is plain that the distribution of peak titres among successes and failures was identical. We next plotted the percentage of measurable titres recorded during the entire period of

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treatment (Fig. 11). With one inexplicable exception, the percentage of measurable anti-staphylococcal serum titres in the cured dogs varied between 50 and 100, as contrasted with 0 to 40% in the failures.

Summary

Clinical experience to date has shown that penicillinase resistant penicillins have earned a secure place in treatment of endocarditis caused by penicillinase producing staphylococci. Treatment should be continued for no less than four weeks. In an experimental model in dogs, data indicate that anti-staphylococcal titres constantly maintained are more important in assuring successful eradication of the staphylococcal infection than occasional high titres. Study of canine lesions also shows that valvular vegetations are sometimes easier to sterilize than infected suture lines.

Data on reported cases, provided through the courtesy of John E. Doyle, M.D., Bristol Laboratories, with the permission of Drs. W. M. M. Kirby, J. Stokes, III, A. C. White, S. Finegold, J. B. Wenzel, L. N. Brodsky, S. Katz, D. B. Louria, T. Sellers, Jr., P. J. Sweeney, A. Becker, and J. E. Geraci.

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TREATMENT OF BACTERIAL ENDOCARDITIS WITH ORAL PENICILLINS

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BEFORE the advent of antibiotics, bacterial endocarditis was almost invariably fatal. The introduction of penicillin altered the prognosis but problems in treatment are still encountered as the organisms are deeply embedded in the heart valves and vegetations. The early and prolonged use of penicillin can now produce a cure in most cases but severe damage to the valves may occur leading to progressive heart failure.

The commonest infecting organism is *Streptococcus viridans*. In 29 consecutive cases we have seen in whom positive blood cultures were obtained this organism was grown in 20 (69%). This organism is usually highly sensitive to penicillin, the minimum inhibitory concentration (or M.I.C.) being 0.03 µg./ml. or less. At the present time the usual treatment of such infections is intramuscular penicillin G.

in a dosage of at least 2 megaunits daily.

Streptococcus faecalis is another frequent organism—it is usually less sensitive to penicillin than *Strept. viridans*, the M.I.C.s of different strains varying between 1.25 and 12.5 µg./ml. Penicillin and streptomycin are often synergistic in their action on this organism and this antibiotic combination has been successfully used. The introduction of α amino-benzyl penicillin or ampicillin provided a new approach to the treatment of *Strept. faecalis* infections as this antibiotic is usually about twice as active against the organism as penicillin G.

Two patients presented with bacterial endocarditis in whom the causative organism was a *Strept. faecalis* more sensitive to ampicillin than to penicillin G or any other antibiotic. Ampicillin controlled the infection in both