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INFECTIVE ENDOCARDITIS: CURRENT TOPICS

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INTRODUCTION

In his recently published book "Infective Endocarditis" Dr. Donald Kaye's opening sentence in the preface states: "Every student of medicine is fascinated by the disease bacterial endocarditis. It has always constituted a disproportionately high percentage of clinical pathological correlations, board examination questions, and grand rounds." Sharing Dr. Kaye's interest I have chosen to discuss infective endocarditis in a limited way, and have selected certain topics which appear of current interest. The topic has not been discussed in our grand rounds since 1969 and it is hoped, therefore, that it will not be disproportionate.

Prior to the era of antibiotics the interest was as great as it is now or perhaps even greater. At that time "SBE" presented as an intellectual exercise, as sort of a clinical workshop for the internist, cardiologist and microbiologist. There was considerable drama in a disease which frequently affected young people and which inexorably progressed to death. The personal emotional impact of this is nowhere better illustrated than in the account of a 4th year Harvard medical student who in 1931 developed subacute bacterial endocarditis and documented his own reactions to the disease. Subsequent to the student's death the account was edited and published by the distinguished clinician Dr. Soma Weiss. (118) The change which came about in 1943-44 when penicillin was first used is difficult even for those involved to remember and is well nigh impossible to appreciate if not actually observed. The change could perhaps be understood if one could imagine today that suddenly a virtually nontoxic drug were to be introduced which would cure two-thirds of the patients with oat-cell carcinoma of the lung.

I do not know who treated the first case of infective endocarditis, but I suspect the first patient was treated by Dr. Henry Dawson at the College of Physicians and Surgeons in New York. Dr. Dawson used crude penicillin made in a microbiology laboratory by Dr. Gladys Hobby. (21) This report appeared in the March, 1944 Journal of the American Medical Association and describes patients treated with doses of 40,000 to 320,000 units of penicillin per day. Five cases were treated and two of them were apparently cured. One of the cured patients received 830,000 units in 10 days and the second received 1.4 million units in 23 days. Following this, a number of cases were treated and reported. It should be noted here that during this war-time period there was a so-called "penicillin czar", Dr. Chester Keefer, who had to approve the use of all of the penicillin in the United States and who initially would not approve its use in the treatment of endocarditis because of the large amount of the drug required. At that time the "massive amounts", in the neighborhood of 5 million units, which were thought to be necessary, could not be justified because of the small supply. Nevertheless, a number of patients were treated, many of the early patients by a physician in Brooklyn who, it was rumored, received his supply of penicillin directly from the benevolent president of one of the pharmaceutical manufacturers. This gentleman used a technique known today in Las Vegas as "skimming" and "smuggled" the penicillin across Brooklyn to avoid the protests of Dr. Keefer. Many developments have occurred in our understanding and our capability of the treatment of infective endocarditis since those relatively primitive beginnings. It is my purpose today to review a number of topics which appear to me to be of current interest, without any attempt to review the disease picture in general.

It is proposed 1) to discuss actual changes in the pathogenesis of infective endocarditis or changes in our understanding of the pathogenesis; 2) to review the changing spectrum of microorganisms known to be involved; 3) to describe important developments in experimental endocarditis which aid in our understanding of its development and treatment; 4) to discuss prophylaxis in the light of new information on sources of bacteremia, as well as the possible impact of studies of prophylaxis of experimental endocarditis; 5) to discuss briefly drug synergism, again with special reference to the findings in experimental endocarditis; 6) the role of new drugs; and 7) the management of complications.

REVIEW ARTICLES

A number of excellent summaries of infective endocarditis have been published, starting with the series of articles in the New England Journal of Medicine by Lerner and Weinstein (62,63,64,65), two excellent summaries by Weinstein and Rubin, and Weinstein and Schlesinger in 1973 (116,117), Cherubin and Neu (15), Kaye (55) and finally the excellent book of Donald Kaye and his co-authors (56).

PATHOGENESIS

Classically, in the early descriptions of infective endocarditis it was noted that the most common microorganisms found were relatively non-pathogenic species, and they were thought essentially always to infect abnormal heart valves. The more acute "pyogenic" organisms such as Staphylococcus and Pneumococcus were thought to do the same, but also to be able to infect normal valves. It has become increasingly evident over the years that these distinctions are invalid, particularly in that the disease frequently develops on endocardium which cannot be recognized to have had prior damage. It was noted by Lerner and Weinstein in 1966

that of 100 patients in their series definite evidence of prior heart disease could not be obtained in 39 patients.

UNDERLYING HEART DISEASE DEMONSTRATED CLINICALLY AND AT AUTOPSY. (1956-1964) (Lerner and Weinstein, 1966)

TYPE OF HEART DISEASE	NUMBER OF PATIENTS
Rheumatic	40
Congenital	10
Atherosclerotic	3
Known Murmur	8
No Heart Murmur	39
Total	100

In another series by Hughes and Gauld (49) there is a description of 68 patients with special reference to the predisposing heart disease.

PREDISPOSING HEART DISEASE IN 68 PATIENTS WITH BACTERIAL ENDOCARDITIS (Hughes & Gauld)

24 cases in "miscellaneous" group
- 19 no prior cardiovascular symptoms
- 9 autopsies
  - 3 atheroma of aortic valve
  - 6 valves normal except for vegetations

As may be seen in this table, of 68 patients there were 24 in a miscellaneous group, 19 of whom had no prior cardiovascular signs or symptoms. Nine of these were autopsied. Three of the nine autopsied had atheromata of the aortic valve and six had valves which were apparently normal except for the presence of vegetations. Specifically with relation to the presence of murmurs, in another series of 70 patients with infective endocarditis (103),

particular reference was paid to the presence of murmurs on admission to the hospital.

PRESENCE OF MURMURS IN 70 PATIENTS WITH INFECTIVE ENDOCARDITIS ON ADMISSION TO HOSPITAL

Infecting Microorganism	Number of Patients Without Murmurs	Total Patients
Penicillin sensitive Streptococci	4	37
Enterococci	3	6
Staphylococci	5	20
Miscellaneous	4	7

Sixteen of the total of 70 patients had no demonstrable murmurs at the time of admission to the hospital, and the presence or absence of murmurs did not appear to relate to any particular type of infecting organism. Another series of 656 patients described by Cherubin and Neu (15) looks at the question in a slightly different way, namely as to whether the patients had any recognized history of heart disease, preexisting diseases likely to cause heart disease, or murmurs.

HISTORY OF HEART DISEASE OR MURMURS IN 656 PATIENTS WITH ENDOCARDITIS (Cherubin & Neu)

Condition	Percentage of Patients
Murmur	24
Rheumatic fever	38.5
Congenital heart disease	5.8
Syphilitic heart disease	1.1
Calcific heart disease	0.2
Denied	29.8

As may be noted here, they again found about 30% of the patients in whom none of the above factors could be implicated.

It has also been noted that the proportion of patients seen in the older age groups is increasing.

CHANGING MORTALITY OF BACTERIAL ENDOCARDITIS
(Great Britain - Hughes & Gauld 1966)

Year	Deaths	Mean Age (Yrs.)	% of cases over 60
1945	716	39	18.4
1951	416	45	26.6
1957	355	52	38.0
1963	344	56	46.8

This is reflected in the changing mortality of endocarditis as recorded in Great Britain (49). In 1945 the percentage of cases over 60 was 18.4%, and this has gradually increased so that in 1963 nearly 47% of the patients were over 60. Similar findings have been noted in this country.

INFECTIVE ENDOCARDITIS OVER 60
(Appelfeld and Hornick 1974)

Total Cases:	136
Over 60	21%
Mortality (over 60)	72%

(In 20 autopsied cases 14 had "normal valves")

As reported by Appelfeld and Hornick in 1974, in a total of 136 cases at the University of Maryland, 21% of the patients were over 60. (5) It is of interest here also that the mortality in this older group was very high, namely 72%, and it is worth noting that of 20 patients in this series autopsied, 14 had normal valves with the exception of the presence of vegetations. Another recent series of cases (102) also stresses the significant aspects of the disease in the older individuals. This study records 42

cases with autopsies in patients 60 years of age or older. It is noteworthy here also that in 14 of the 42 patients no underlying valvular disease could be demonstrated. It was stressed in this series that the clinical suspicion for the presence of endocarditis was very low and only 40% of the cases had adequate data recorded in the clinical chart.

Another recent development of great interest is the recognition that infective endocarditis develops in the "click-murmur" syndrome. As you know, in recent years the click-murmur has been recognized as a very common finding in individuals who otherwise appear to be normal. It has been estimated by some as occurring in as many as 10% of the population. It is also a finding which is intermittent and which is readily missed on ordinary physical examination. These two facts become of particular importance as we will see later in the consideration of prophylaxis. A good description of infective endocarditis in this syndrome has been published by Lachman and his associates. (60) They described 10 patients with the billowing mitral leaflet syndrome who developed infective endocarditis. Seven of the 10 patients were unaware of their cardiac lesions. In 4 the auscultatory features were difficult to detect, in that they were intermittent, soft, or brought out only with postural changes. The fact that this syndrome is so common and that so few cases have been recognized to have developed infective endocarditis has raised the question of whether the frequency of endocarditis warrants the routine use of prophylaxis in these patients when they are recognized. Allen and associates (1) have a study of special interest in this respect.

SIGNIFICANCE AND PROGNOSIS OF AN ISOLATED
LATE SYSTOLIC MURMUR (Allan, et al 1974)

Total Patients	62
Years Followed	9-22 (average 13.8)
Bacterial Endocarditis	5

These authors reported on 62 patients with isolated late systolic murmurs who were followed between 9 and 22 years with an average of nearly 14 years followup. In that time, five of the 62 patients had developed bacterial endocarditis and although these figures are difficult to compare with those related to other specific cardiac lesions, it seems certain that this represents a high frequency.

Another lesion now recognized to be associated with infective endocarditis is idiopathic hypertrophic subaortic stenosis. Weinstein and Rubin (116) state that 5% of individuals with this syndrome develop infective endocarditis. The location of the endocarditis lesion is of special interest. In one case, (76) the lesion was on the aortic valve which appeared to be normal except for the vegetation. In another group of five patients recently reported (108) one patient was found at autopsy to have vegetations on the mitral valve. One had mitral insufficiency clinically but no postmortem examination was available. The third also had mitral insufficiency clinically and was cured.

DRUG ABUSE

Infective endocarditis is now well recognized as a serious complication in drug abusers. The mechanism of this is presumed to be the development of bacteremia secondary either to local abscess formation or to septic

thrombophlebitis at the site of intravenous injections. Cherubin and his associates published an interesting review of their experience. (14)

OCCURRENCE OF ENDOCARDITIS IN DRUG ADDICTS
(Cherubin, et al 1968)

"Minimum" Incidence	1.4 cases/10,000 addicts/yr.
Death rate N.Y.C. (all cases)	0.045/10,000/yr.
Incidence in young adults with chronic rheumatic heart disease	0.4/10,000/yr.

These authors estimate the minimum incidence of infective endocarditis to be 1.4 cases per 10,000 addicts per year. The death rate from endocarditis in New York City was estimated at .045 cases per 10,000 per year. If one assumes the general mortality to be 40%, this would calculate an incidence of the disease in the general population as 0.11 cases per 10,000/year; or about 1/12th that in drug addicts. The incidence in young adults with chronic rheumatic heart disease is only about one-fourth of that noted in drug addicts. The disease presents some interesting features in comparison with infective endocarditis in general. (61) It occurs in a young age group, the frequency of tricuspid valve involvement is common, and the frequency of pre-existing valve disease is low. When right-sided disease is involved, the clinical picture is dominated by repeated episodes of septic pulmonary infarction. The pathogens are extremely variable and appear to have an unusual type of regional distribution, suggesting that common sources of the drug may have a common source of infection. For example, in Cleveland 11 of 20 cases were caused by enterococci. (82) In Chicago in a study of

23 cases 70% of the cases were caused by Staphylococcus aureus. (8) A similar percentage of staphylococci was noted in a series from New York (100) and Washington. (8) Earlier reports stressed the frequency of Candida in these patients. In a series from Detroit ten of 25 patients were infected with Pseudomonas. (30) In another series from San Francisco (71) Serratia marcescens was common. Two studies are of special interest. Hall et al (45) reported two heroin addicts, a husband and wife, who shared injection paraphernalia and both developed enterococcal endocarditis within a short space of time. The two strains appeared to be identical.

In contrast with the common concept that the drugs themselves are contaminated by the microorganisms, is the report by Tuazon and Sheagren. (106) In a series of ten patients with drug related staphylococcal endocarditis it was found that in all cases the patients were carriers of Staphylococcus aureus and in each case the bacteriophage type of the carried organism matched that of the organism recovered from the blood.

Menda and Gorbach (70) presented a representative series.

DATA ON 23 HEROIN ADDICTS WITH BACTERIAL ENDOCARDITIS
(Menda & Gorbach 1973)

Microorganisms		Valves Involved	
Staphylococcus aureus	16	Tricuspid only	11
Str. fecalis	3	Tricuspid & aortic	1
Viridans streptococcus	2	Mitral	2
Pseudomonas	1	Aortic	1
Mixed	1	Mitral & aortic	5
		Congenital	3

Here it will be noted that Staphylococcus was the most common microorganism and the tricuspid was the most commonly involved valve. Data on a large group of heroin addicts has also been reported by Banks et al. (8)

ENDOCARDITIS IN HEROIN ADDICTS (Banks, et al 1973)

Total Cases:	50 (8% of addicts admitted)
Positive Blood Cultures	39
Pulmonary Embolism	32
Solitary Tricuspid Valve Involvement	36 (72%)
Cases Caused by Staphylococcus	28 (56%)

A total of fifty cases are reported, representing 8% of the admissions of drug addicts. They noted, as in other series, that pulmonary embolism and infarction were common manifestations, occurring in 32 patients. Solitary tricuspid valve involvement was also frequent. Again, staphylococci were the most common organisms. Although we will not discuss in detail the question of treatment of right-sided bacterial endocarditis, the data recorded in reference 69 are worthy of review. This report concerns 25 patients with right-sided bacterial endocarditis, 23 of whom were heroin addicts. These authors noted that when infection was due to gram positive cocci, antibiotics were capable of curing the patient. However, if the infection was due to Pseudomonas aeruginosa, they were resistant to therapy and excision of the infected tricuspid or tricuspid and pulmonary valves without prosthetic replacement effected cures. Nine out of ten long term survivors treated in this manner had no significant hemodynamic difficulties. It should be noted that not all of the reports of infective endocarditis in narcotic addicts have listed tricuspid valve involvement this frequently. This is notable in the report of Cherubin and associates. (14) These authors found only three cases of isolated tricuspid disease in a total of 36 patients.

PROSTHETIC VALVE ENDOCARDITIS

Since the introduction of surgery for valvular and congenital heart disease, it has been recognized that a certain risk of infective endocarditis

is incurred in all types of intracardiac surgery. As more experience has been gained, a somewhat clearer perspective is possible. Because of the fact that a variety of infections occur in these patients, many of which are associated with bacteremia and virtually all associated with fever, it becomes important to differentiate those patients who have prosthetic cardiac valve infections. Sande and his associates (93) have provided evidence of value in this respect. They studied 22 patients with prosthetic heart valves who had 24 episodes of sustained bacteremia. As pointed out in this article and in the accompanying editorial (115), the data are clear that the development of sustained bacteremia after valvular surgery does not necessarily mean infection of the prosthesis. The first important consideration appeared to be the interval between the operative procedure and the bacteremia. A period of less than 25 days was more often associated with lesions outside the heart, whereas a longer one (generally 60 days or more), was more consistent with infection of the prosthesis. Second, the appearance of new murmurs suggested infection of the prosthesis. Third, detectable evidence of extracardiac sources of bacteremia such as sternal infection, the presence of transvenous catheters, pneumonia, suppurative phlebitis, etc., made involvement of the prosthetic valve less likely. Fourth, the common clinical observation that gram negative bacilli in the blood usually don't come from the heart valve still obtained in this series. Fifth, it was noted that most of the organisms isolated from the blood in cases of infected prostheses were sensitive to the prophylactic antimicrobial drug, but those isolated from patients with extracardiac infections were usually resistant to the drug. This is probably again a reflection of the

frequency of gram negative bacilli in this latter group. A number of other articles may be referred to. (3,46,67,83,93,115,122) A recent report details well some of the aspects of prosthetic endocarditis of the aortic valve, the most common of all. (67)

PROSTHETIC VALVULAR ENDOCARDITIS OF AORTIC VALVE (I)
(Madison, et al 1975)

Total - 16 patients (8% of prosthetic aortic valves)
Mortality = 69%
Microorganisms:

Staph Aureus	4
Staph Epidermidis	4
Streptococci	2
Enterococci	2
Candida	2
Pseudomonas	2

This report summarizes sixteen patients representing 8% of the prosthetic aortic valves. The mortality in this group was 69%. The microorganisms were for the most part gram positive cocci, with two cases due to Candida and two due to Pseudomonas.

PROSTHETIC VALVULAR ENDOCARDITIS OF AORTIC VALVE (II)
(Madison, et al 1975)

Aortic insufficiency developed in 11 patients
Antibiotic treatment alone - 10 (4 cured)
Antibiotic plus reoperation - 6 (2 cured)

In these sixteen patients, eleven developed aortic insufficiency. Ten patients were treated with antibiotics alone, of whom four were cured. Six were treated with antibiotics plus reoperation, of whom two were cured. Another excellent summary is recorded in reference 122.

PROSTHETIC VALVE ENDOCARDITIS I (Wilson et al 1975)

Total Cases - 45 in 4586 patients (1%)

Early Onset (i.e. <2 months)	16
Late Onset	29
Mortality = Overall	56%
= Early Cases	88%
= Late Cases	40%

This report details the findings in 45 patients representing 1% of the total patients having prosthetic valves. Of these, sixteen had the onset less than two months after surgery. Again, as noted by Sande, the frequency of late onset of endocarditis was greater. The mortality in these patients was 56%, but the mortality in the early cases as has been repeatedly noted, was much higher.

PROSTHETIC VALVE ENDOCARDITIS II (Wilson et al 1975)

Results of treatment in 45 cases
Medical therapy alone: 12 cures
Combined medical & surgical: 8 cures

In this same group of patients, 20 patients of the 45 were cured; 12 were cured with medical therapy alone and eight were cured with combined medical and surgical therapy.

TRANSVENOUS CATHETERS

The widespread use of transvenous catheters of various types has been recognized as a significant hazard of infection. The best recognized of these situations is in patients receiving total parenteral nutrition, and in them the frequency of infection has probably been related to the long time the

transvenous catheters were in place. Goldmann and Maki have reported on this problem, and their article gives a good bibliography. (39) It is difficult to estimate the exact hazard involved with the usual small catheters used for intravenous fluid administration. That it is a risk of bacteremia is without question. Greene et al (43) have attempted to estimate the risk of endocarditis in a group of patients having indwelling pulmonary artery catheters. The risk here is probably considerably greater than that involved with a catheter in a peripheral vein.

RISK OF RIGHT-SIDED ENDOCARDITIS IN USE OF INDWELLING PULMONARY ARTERY CATHETER (IPA) (Greene et al 1975)

493 autopsies in 30 months before IPA use
1 thrombotic endocarditis
438 autopsies in 30 months of IPA use
1 thrombotic endocarditis (no catheter)
2 thrombotic endocarditis CVP catheter
4 thrombotic endocarditis IPA catheter
3 infective endocarditis CVP catheter
1 infective endocarditis IPA catheter

These authors reviewed 493 autopsies in the Letterman Army Medical Center in the thiry months before the use of indwelling pulmonary artery catheters (IPA). In that group there was only one case of thrombotic endocarditis. In the thirty months subsequent to the use of indwelling pulmonary artery catheters, 438 autopsies were performed. One of these had thrombotic endocarditis, but that patient had not had a catheter. Two had thrombotic endocarditis and had had catheters to measure central venous pressure. Four had thrombotic endocarditis resulting from IPA catheter. There were two cases of infective endocarditis related to central venous

pressure catheters and one due to an IPA catheter. On the basis of the experience with experimental endocarditis it is assumed that the thrombotic endocarditis may be an important antecedent of infective endocarditis and also that trauma to the valve (which theoretically does not occur with central venous pressure catheters) is also an important antecedent. A relatively new but uncommon source of difficulty is also found with transvenous cardiac pacemakers.(18)

Another risk factor in the development of endocarditis which needs to be considered is the intrauterine device. At the present time it is estimated that 2.5% of patients develop uterine infections within the first year after placement of IUD's. One case of group B streptococcal endocarditis has been reported secondary to an IUD. (17) Although this remains a controversial point, it would appear that the presence of valvular or congenital heart disease should be a relative contraindication to the use of an IUD if other effective birth control methods are available. (53)

ACCESS SITES

An excellent review of the problem of access site infections in hemodialysis patients has been published recently by Cross and Steigbigel. (19) It is pointed out that infection is the second leading cause of death in patients on repetitive hemodialysis and that the access sites are the most common sources of infection. Endocarditis represents one of the types of infection encountered. In their review of the literature they found more episodes of infective endocarditis in patients with AV cannulas than in those with AV fistulas. The most commonly reported microorganisms were staphylococci. These authors described infective endocarditis as "a subtle and often lethal complication of hemodialysis". They report a total of 35 episodes described to date.

A report from this department describes 5 patients with staphylococcal sepsis on chronic hemodialysis. (9) This article presents a good description of the clinical features of the disease and reports the interesting capability of treating patients once or twice a week with vancomycin, taking advantage of the poor renal function to sustain adequate levels of the drug.

UNUSUAL MICROORGANISMS

Candida: The current problems with Candida infections are unfortunately becoming all too familiar. Prolonged use of steroids, antimicrobial drugs, transvenous catheters and immunosuppressive agents has led to a tremendous increase in the frequency of superficial Candida infections as well as to more deep-seated systemic disease associated with candidemia. (31,39) An excellent review of Candida endocarditis has been reported in 1975 by Rubenstein et al. (89)

FUNGAL ENDOCARDITIS (I) (Rubenstein et al 1975)

Characteristics in Non-Addicts

- Most common in patients with cardiac surgery
- Common with prolonged intravenous fluid and antibiotic therapy (especially treatment of bacterial endocarditis)
- Candida albicans and Aspergillus most common

These authors pointed out the difference between the disease in addicts and non-addicts. In non-addicts it was most common in patients who had had cardiac surgery. It also occurred with prolonged intravenous fluid and antibiotic therapy. In this connection it is unfortunately true that a significant number of the cases have arisen in patients being treated for bacterial endocarditis. This event, namely the occurrence of Candida endocarditis in a patient who is under therapy for some readily curable

type of bacterial endocarditis, is indeed a tragic circumstance, and it must be admitted it is generally preventable. These authors point out that Candida albicans and Aspergillus are the most common fungi in the non-addicts.

In addicts, other Candida are more common.

FUNGAL ENDOCARDITIS (II) (Rubenstein et al 1975)

Characteristics in Addicts

Candida albicans	1
Candida parapsilosis	17
Candida guilliermondi	4
Candida stellatoidea	4
Candida krusei	3
Other	6
Total	35

As noted here Candida albicans was relatively infrequent, occurring in only one of 35 patients, and Candida parapsilosis was found in approximately half of the patients.

Although potent antifungal drugs, amphotericin and flucytosine, are available for the treatment of fungal endocarditis, the mortality rate is at least 80% and probably even higher. The problem in estimating mortality lies in the difficulty in actually making the diagnosis. Certainly the presence of candidemia in a patient with a heart murmur, especially with a prosthetic valve, makes the diagnosis of endocarditis likely. It is not a certainty, however, and perhaps some of the patients who have been reported as cured may not actually have had endocarditis. Certainly, peripheral venous or arterial sources of Candida sepsis may be found with or without endocarditis. (38)

The potential use of surgery was reported by Kay in 1961 and further experience was reported by him and his associates in 1968. (54) On the basis

of their experience they have recommended that all patients with Candida endocarditis be treated both with amphotericin and with surgery where surgery is possible. They recommend both intraoperative and postoperative therapy with amphotericin. Montague and Sugg (75) have reported an interesting patient from this institution, a patient with Candida endocarditis who was cured with surgery and flucytosine.

Serratia: Endocarditis due to Serratia has been reported in patients with prosthetic valves, but most of the patients reported have been drug addicts. (58,71,94)

SERRATIA ENDOCARDITIS (Mills & Drew, 1976)

Total cases: 19 Addicts: 17
Left-sided disease: 13
12 treated with antibiotics - all died
1 surgery and antibiotics - cured
Right-sided disease: 6
5 treated with antibiotics - 4 cured
1 surgery and antibiotics - cured

Mills and Drew reported (71) what they considered a "regional illness" associated with intravenous drug abuse. In 1976 they found only twelve cases of Serratia infection of natural heart valves in the literature. They themselves collected 19 cases in a period of five years in the San Francisco Bay area. Seventeen of these were drug users. Thirteen of the patients had left-sided disease. Twelve were treated with antibiotics and all died. The one cure was in a patient who received both antibiotics and surgery. Of the six patients who had right-sided disease, four were cured with antibiotics alone and one with antibiotics plus surgery. Carbenicillin, gentamicin and chloramphenicol are the drugs which apparently have been most successfully used.

Pseudomonas: In a review of the problem of Pseudomonas endocarditis in 1973, Saroff, Armstrong and Johnson (95) reported one case in a heroin addict and reviewed the literature.

PSEUDOMONAS ENDOCARDITIS I (Saroff et al 1973)

Associated Cardiac Conditions	
Rheumatic heart disease	5
Cardiac surgery	18
Previous bacterial endocarditis	2
Other heart disease	4
Unspecified	17
Total	46

The associated conditions in these 46 patients were rheumatic heart disease in five, prior cardiac surgery in 19, prior bacterial endocarditis in two, four with other heart disease, and 17 non-specified.

PSEUDOMONAS ENDOCARDITIS II (Saroff et al 1973)

Cures:

1) Polymyxin + sulfadiazine + surgery
2) Polymyxin + colistin
3) Polymyxin + tetracycline + surgery
4) Polymyxin + colistimethate + cephalothin
5) Polymyxin + colistimethate + kanamycin
6) Polymyxin + gentamicin + carbenicillin

Only six patients were cured, including Saroff's case. It is of interest that all of the patients cured had received polymyxin. Whether this reflects merely the fact that the drug has been around longer is uncertain. It again raises the same issue as we noted previously with fungal endocarditis and with Serratia endocarditis, namely that antimicrobial chemotherapy is generally not successful and it is quite likely here also an aggressive approach to

surgery should be advocated.

Rickettsia: The occurrence of endocarditis due to Rickettsia, specifically Coxiella burneti, has been known since at least 1960, but in this country it remains a curiosity which we read about but thus far fail to identify. It is presumably much more common in the areas of the world where Q-fever is more common, and indeed in 1976 Wilson and his associates from Australia (121) reported a total of thirteen cases with proven, and three with probable, endocarditis. This article plus reference 16 summarize the clinical features of this disease.

ENDOCARDITIS DUE TO COXIELLA BURNETI (Wilson et al 1976)
16 cases in Queensland

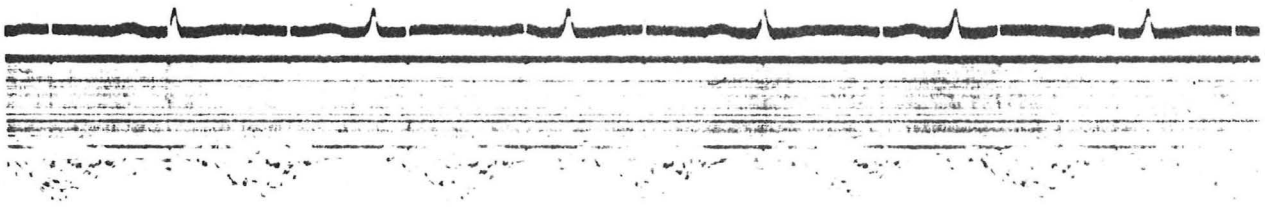
Time from onset of fever to endocarditis - up to 20 years
Diagnosis: Microscopy of valve
Isolation of organism (animal inoculation)
High antibody titer to phase I antigen
$\geq$ 1:256 (3 cases)
Cures: Antibiotic - 1
Antibiotic + Surgery - 10

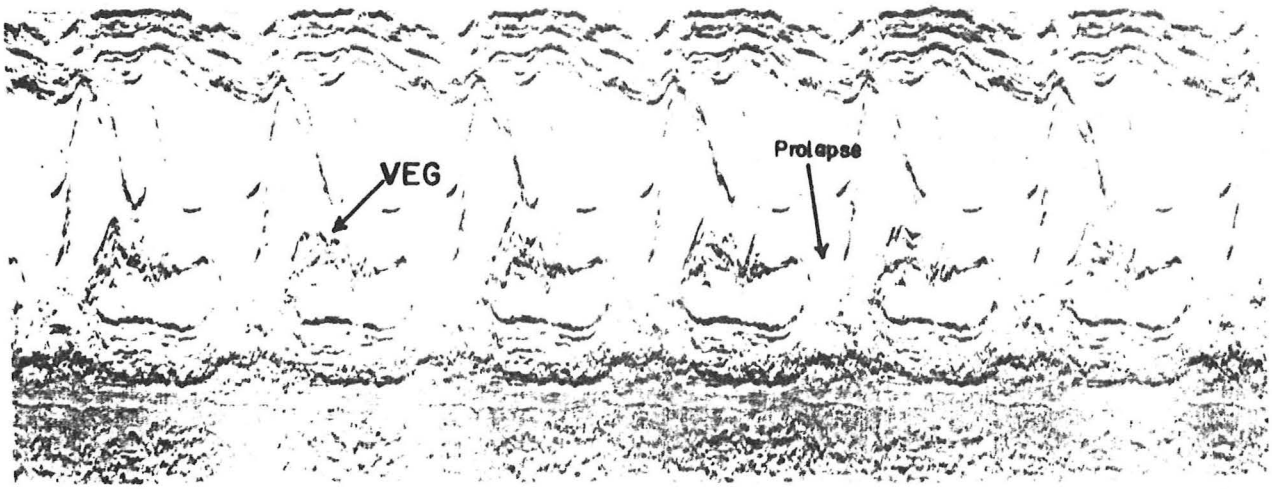
The first and most interesting aspect of it is that there is apparently a long time between the initial development of Q-fever and the development of endocarditis, in some cases up to 20 years. The diagnosis is made either by microscopy of the valve, isolation of the organism in cultures of tissue removed at autopsy or operation, or on the basis of high antibody titers in phase I antigen. Apparently all of the cases have had antibody titers of over 1:256 to phase I antigen. As we have noted with some of the other microorganisms, cure with antibiotics is apparently very unusual and in this series included only one patient. Ten of the patients had surgery together with antibiotics, usually tetracycline or chloramphenicol, and were cured. (16,47,110,120,121)

Non-enterococcal Group-D streptococci: Within recent years the introduction of a new culture medium into routine bacteriology has led to the separation and identification of non-enterococcal Group D streptococci. On primary isolation almost all group D streptococci produce black colonies on bile-eschulin medium. One further step in the laboratory is required to separate the enterococci, (usually Streptococcus fecalis), from the non-enterococcal group D streptococci (usually Streptococcus bovis). The distinction is of clinical importance in that Streptococcus bovis is penicillin sensitive and is treatable with ordinary doses of penicillin. Enterococci, in contrast, require treatment with large doses of penicillin and with an aminoglycoside. (74,112)

DIAGNOSTIC TECHNIQUES

The use of the echocardiogram is an additional potential diagnostic technique in the visualization of vegetations in patients suspected of endocarditis. (6,22,40,41,48,69,111) It is difficult to reproduce these in the protocol but perhaps this one will be satisfactory.





This is from one of our own patients and shows a vegetation on a prolapsed mitral valve. The journal references give a number of good illustrations. Although echocardiography at present has limited usefulness, it at times contributes greatly to the clinical information. At least one report (123) suggest that Gallium scanning of the heart may also make it possible to visualize vegetations. Echocardiography and phonocardiography may be used to assess the severity of acute aortic insufficiency in the preoperative evaluation of patients. (68)

Miscellaneous: No outstanding developments related to endocarditis have appeared in microbiology in the past few years. Powers and Mandell (82) have reported finding intraleukocytic bacteria in leukocyte monolayers from patients of suspected endocarditis. The usefulness of this technique is uncertain, but probably is limited. One report suggests an interesting technique of differential quantitative blood cultures on either side of the values as a means of preoperatively localizing the site of infection. (78)

Additional reports have appeared on the clinical use of the serum bactericidal test, but have not truly clarified its validity. (10,28) A number of reports of items of special interest may be cited. First, a report by Gould and others (42) from this department describes an interesting observation that microorganisms which most frequently cause bacterial endocarditis were found to adhere best to heart valves in vitro, suggesting that the ability to adhere to valvular endothelium may be an important or essential characteristic of bacteria which cause endocarditis in man.

The determination of teichoic acid antibodies in patients with suspected staphylococcal endocarditis is of interest. (20,107)

TEICHOIC ACID ANTIBODIES
(Tuazon et al 1976)

Diagnosis	Number of Patients	Teichoic Acid (Antibodies (CIE)
Staph endocarditis	28	28
Staph bacteremia	15	8
Staph osteomyelitis	5	3
Staph abscesses	8	1
Non-staph infections	20	0

In a study by Tuazon and Sheagren(107) all of the patients with proven staphylococcal endocarditis had positive teichoic acid antibodies by the counter-immunoelectrophoresis technique. Patients with staphylococcal bacteremia of other sources had considerably fewer positives. Thus, in this study, the absence of teichoic acid antibodies would have been a finding suggesting strongly that staphylococcal endocarditis was not present.

Further clarification of the renal lesions in infective endocarditis has been published. In addition simply to emboli to the kidneys, there may be focal embolic glomerulitis, acute and chronic glomerulonephritis. It appears clear that immune complexes are formed in patients with endocarditis, especially those cases of some duration, and it has been demonstrated that immune complexes are deposited in the basement membrane of glomeruli, strongly suggesting an immunologic basis for this type of renal involvement. (44,56a,81) Renal failure is unusual in endocarditis, but it is relatively common when diffuse glomerulonephritis develops. The renal lesion may be partially, but often not completely, reversible with effective antimicrobial therapy.

The fact that circulating immune complexes have been demonstrated in endocarditis (44) has led to speculation that some of the peripheral lesions, such as Osler's nodes and subungual hemorrhages, may actually be due to vasculitis.

Indeed, many of the older studies of such lesions have emphasized the absence of microorganisms and the presence of vasculitis. On the basis of present evidence it is likely that three types of lesions are represented peripherally: 1) vasculitis due to deposition of immune complexes. 2) simple microemboli without organisms or with organisms which cannot multiply locally. 3) microabscesses together with emboli. (2,44)

Rheumatoid factor is present in the serum of 20-50% of patients with infective endocarditis and in general is correlated with the duration of the disease. (97)

Serum cryoglobulins were found in 19 out of 20 patients with infective endocarditis. (51) The cryoglobulins were of the "mixed type" consisting of IgG, IgM, and IgA. C3 and fibrinogen were present in some instances. IgM rheumatoid factor was present in the cryoglobulins. These findings were considered consistent with the view that cryoglobulins represent circulating immune complexes which may be important in the pathogenesis of some of the immunologic sequelae in patients with infective endocarditis.

EXPERIMENTAL ENDOCARDITIS

Models for the production of experimental endocarditis are not new. Indeed, it is of historical interest to note that in 1912 there had been so many papers written about it that the Russian investigator Saltykow was moved to publish a review of the topic. (52) These early investigators made a number of interesting observations. In general they found that it was difficult to produce endocarditis in animals with any regularity although it could be done at times simply by the intravenous injection of cultures. Direct trauma to the valves or what they thought was probably indirect trauma produced by the intravenous injections of such things as potato fragments, pieces of

coal dust, etc., together with the injection of microorganisms made the production of endocarditis more regular. Although these papers are of great interest historically, a good model for the laboratory production of endocarditis was first described by Freedman and associates in 1970, and their subsequent work is summarized in reference 33. It had been observed that certain manipulations such as the production of AV shunts, exposure of animals to high altitude chambers and the production of lymphatic obstruction all predisposed to the development of experimental endocarditis. All of these stresses had in common some type of non-bacterial lesion of the heart valves. In 1970 and in subsequent articles Freedman and his associates, in a series of papers in the Yale Journal of Biology and Medicine, described the model which is now generally used. (33,34)

Plastic catheters are passed into the right or left side of the heart of rabbits and allowed to remain in place. These are followed by injections of various microorganisms and result regularly in the production of infective endocarditis. Typical vegetations are present on the endocardium. Titers of bacteria in vegetations on the left side of the heart regularly are 10^9-10^{10} organisms per gram of vegetation. Somewhat lower concentrations, 10^7 or 10^8 per gram of tissue are found on the right side. It was noted in early studies that there was a considerable tendency for the lesions on the right side of the heart to heal, but that once left-sided disease was established, the animals usually died. It was noted by Freedman that if the catheter was removed before microorganisms were injected, infection became progressively more difficult as time passed. It was also noted that large inocula of microorganisms were necessary to produce the disease regularly.

In a further series of study by Durack, Beeson, Petersdorf and Pelletier (24,25,26,27,79,81) additional observations were made. It was noted that positioning of the catheter across the valve produced a nonbacterial thrombotic endocarditis. When this was followed by the intravenous injection of microorganisms, most of the animals died of infective endocarditis.

EFFECT OF INOCULUM SIZE ON INCIDENCE OF
BACTERIAL ENDOCARDITIS IN RABBITS WITH RIGHT-SIDED CATHETERS
(Durack et al 1973)

Number (str viridans)	Number infected/total
10^8	28/28
10^6	3/4
10^4 - 10^5	4/9
10^2 - 10^3	1/4

Injection of 10^8 microorganisms regularly produced infection and as the inoculum size decreased, as it shown in the table, there was a progressive decrease in frequency of infection. Utilizing autoradiographic techniques it was shown that the surface organisms remained metabolically active, the deeper organisms less so. As in earlier studies, it was noted that despite trauma to the valve, if the catheters were withdrawn, infection was more difficult to achieve. As previously mentioned, without the catheter, even with multiple injection of microorganisms, fewer than one-third of the animals became infected. It was not possible to produce the disease with L-forms or with viruses. Similar models have been developed in dogs for both staphylococcal disease and enterococcal disease. (57) Sande (56) noted that prior administration of anticoagulant drugs prevented the development of nonbacterial thrombotic lesions but actually did not prevent the disease. Infection appeared to be actually more severe under these circumstances in terms of its clinical manifestations but was actually easier to cure with antimicrobial drugs. Other studies (34) demonstrated the capability of producing the disease with Candida and, surprisingly, it was noted that

this was a relatively benign disease in the animals.

These investigators and others, having defined a means of production of the disease, have attempted various maneuvers in determining optimal prophylaxis and treatment.

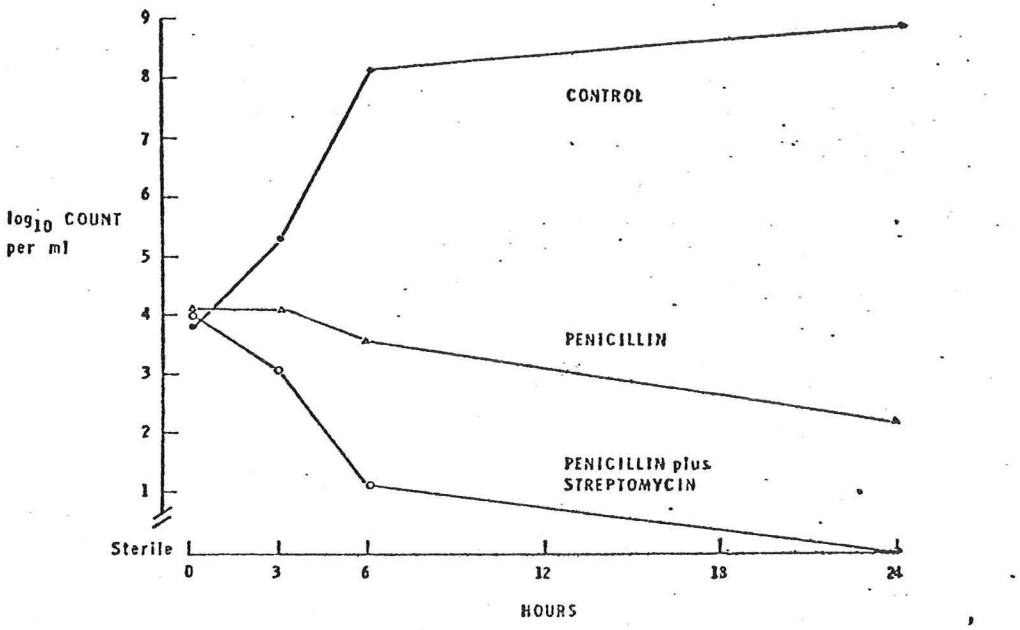


FIGURE 4 Comparison of the bactericidal action of penicillin alone with penicillin plus streptomycin, against penicillin-sensitive *Streptococcus viridans* in vitro.

On the basis of studies such as the growth curves shown in the above figure, (124) it had been known for many years that penicillin, although normally labeled a "bactericidal" drug, frequently did not reduce the number of microorganisms in this system to zero. The 100 to 1000 organisms per ml. remaining in these cultures exposed to penicillin are not "resistant" to penicillin in the conventional sense of the word, but have been labeled "persisters". It has also been known that penicillin together with streptomycin will usually be more completely bactericidal in vitro as shown in this figure, even though the organism is not "sensitive" to streptomycin by conventional testing. This combination of drugs as well as others were utilized in a variety of studies.

ATTEMPTED PROPHYLAXIS OF EXPERIMENTAL STR. VIRIDANS ENDOCARDITIS (Durack & Petersdorf 1973)

	MG/KG	% Protected
Penicillin G	150	9
Ampicillin	30	20
Cephaloridine	30	17
Vancomycin	30	100
Penicillin plus Streptomycin	150 15	100

In their initial studies of prophylaxis, Durack and Petersdorf (26) used penicillin G in a single dose and found that only 9% of the animals were protected. Ampicillin and cephaloridine were likewise ineffective, but either vancomycin or penicillin plus streptomycin were protective.

SINGLE DOSE PROPHYLAXIS Rabbits - 10^8 Str. Viridans (Pelletier et al 1975)

Drug	Dose Mg/Kg	% Protected
Penicillin	30 IM	18
Ampicillin	30 IM	15
Cephalexin	30 IM	0

In further studies (79), similar poor protection was found with penicillin V, ampicillin again and cephalexin. Multiple dose prophylaxis in rabbits, however, produced somewhat different results as indicated in this table.

MULTIPLE DOSE PROPHYLAXIS IN RABBITS
Str. Viridans 10^8 (Pelletier et al 1975)

Drug	Dose Mg/Kg	Frequency	% Protected
Penicillin V	7.5 IM	q 6 h x 8	20
Penicillin V	30 IM +7.5 IM	1 q 6 h x 4	100
Erythromycin	15 IV	q 6 h x 8	36

As will be noted in the second line, penicillin given with a loading dose and every four hours for four doses resulted in 100% protection. It is noteworthy here that erythromycin in multiple doses was also ineffectual.

PROPHYLAXIS IN RABBITS STR. VIRIDANS $10^{5.4}$
(Pelletier et al 1975)

Drug	Mg/Kg	Frequency	% Protected*
Penicillin V	7.5 IM	q 6 h x 8	71
Erythromycin	15 IM	x 1	90

*Controls = 60% infected

Of particular interest is the response in animals infected with a smaller inoculum of organisms. This is not necessarily strictly of academic interest. The level of bacteremia which occurs after procedures such as dental extractions, etc. is really quite low, and it is thus quite possible that results obtained in animals infected with small inocula may be more directly applicable to the clinical situation than are the others. In this same set of experiments using an inoculum of $10^{5.4}$ it was noted that 60% of control animals were infected. The same dose of penicillin V which was ineffectual in preventing infection with the larger inoculum was reasonably successful here and provided protection of 71% as compared with the control. That is to say, 29% of the animals developed infection as compared to 60% of the controls. Surprisingly, erythromycin in a single dose permitted infection in only 10% of animals as compared with 60% of the controls.

Additional studies directed towards cure of infections (80,92,98) have demonstrated that rabbits with catheter induced aortic valve endocarditis caused by Streptococcus viridans were more effectively treated with penicillin plus an aminoglycoside (streptomycin or gentamicin) than with penicillin alone.

Using a penicillin-aminoglycoside combination bacteria were eradicated from cardiac vegetations in approximately one-half the time or less required with penicillin alone.

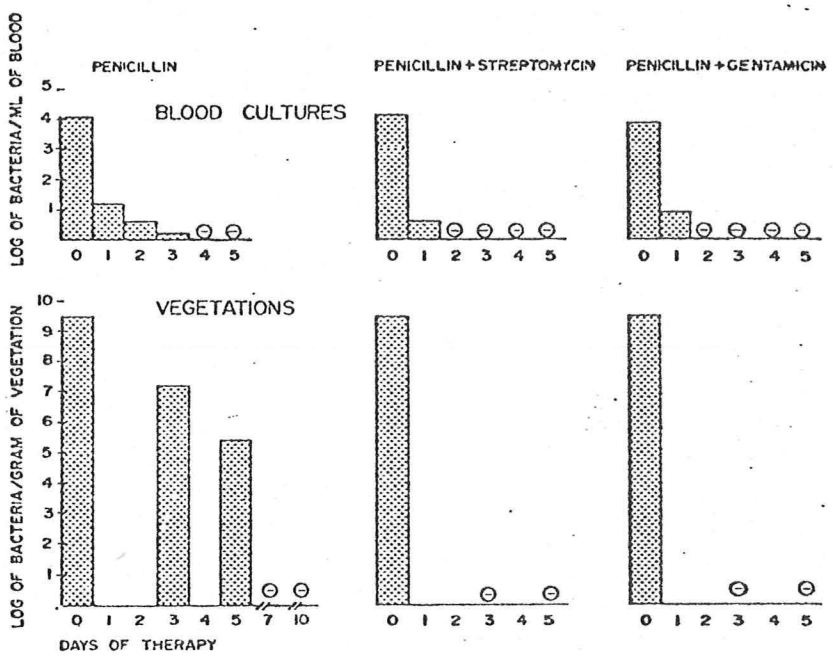


Figure 3. Results of blood and vegetation cultures from rabbits with *S. viridans* endocarditis treated with penicillin alone, penicillin plus streptomycin, or penicillin plus gentamicin.

As seen in this figure from Kaye's book, elimination of organisms from the vegetations (lower half of figure) occurred after one day of combined therapy as compared with over five days with penicillin alone. It was shown also that an increased delay between infection and initiation of treatment lengthened the period of therapy necessary to effect a cure. Irrespective of the interval between infection and the onset of therapy, however, the combination of penicillin and streptomycin consistently showed superior invitro bactericidal activity as compared with penicillin alone, and regularly eliminated streptococci from endocardial vegetations more rapidly than penicillin alone. These observations are entirely in accord with prior clinical observations.(104,126)

Some familiarity with the general nature of studies on experimental

endocarditis seems particularly important at the present time. A number of extrapolations are being made to the clinical situations concerning treatment and prophylaxis, some of which, such as the above, appear to be very well founded. Others appear to conflict seriously with clinical experience and thus bear careful scrutiny. To summarize the situation, the series of experimental studies to date appear to show the following. (12,13, 24,25,27,33,34,57,79,81,91,124)

1. The experimental model provides a regularly reproducible model which in most respects has the clinical and pathological picture of infective endocarditis in man.
2. The model appears to provide an exceptionally good framework for the study of drug action. This is especially important in reference to prophylaxis, because in the clinical setting it is virtually impossible to get such information.
3. The experimental data to date appear in general very sound and the correlations with well recognized clinical facts are good; e.g. the effectiveness of penicillin in treatment, the generally superior performance of so-called bactericidal drugs, and the higher potency achieved through the combined action of penicillin and an aminoglycoside in the treatment of viridans and enterococcal endocarditis.

There are some problems in making any direct correlations between the animal disease and human disease, and one should be aware of these.

1. This is a very acute disease in the animals, even in the animals infected with viridans streptococci. Regardless of whether one allows the catheters to remain in place in the heart or not, the infective inoculum is extremely high and any inoculum which approximates the low level of bacteremia usually seen in man is generally unsuccessful even in infecting the animals.

2. There is considerable tendency for the disease produced on the right side of the heart to heal spontaneously, and although one cannot state categorically that this is not the case in humans, it seems unlikely.
3. Cures are effected with very brief courses of therapy; for example, 5-7 days.
4. Many of the reported differences in effectiveness of drugs in the treatment of experimental endocarditis are based on the colony count in the vegetations within the first few days, and in a number of very significant instances, these differences did not continue as the experiments progressed. For example, (13) antagonism between chloramphenicol and penicillin in the treatment of streptococcal endocarditis in rabbits has been reported. The conclusion that there was antagonism was based on the colony counts in the vegetations 2-3 days after the start of therapy. Despite this fact, all of the animals were curable with the combination.

One other set of studies concerning combined drug action in vitro and in experimental endocarditis has important clinical relevance and I would like to examine these in more detail. In early studies of penicillin action it was noted that enterococci were uniformly resistant to penicillin. Observations on the treatment of enterococcal endocarditis suggested that penicillin therapy alone was generally inadequate. It was not always unsuccessful, but frequently so. Since these reports in 1950 and 1951 (50,88) of the effectiveness of combined therapy with penicillin and streptomycin, this type of therapy has been fairly routine. With this employed as standard therapy very few failures have been reported.

Among the early studies of the synergism of penicillin and streptomycin

the following type of curves were noted with penicillin-sensitive streptococci.

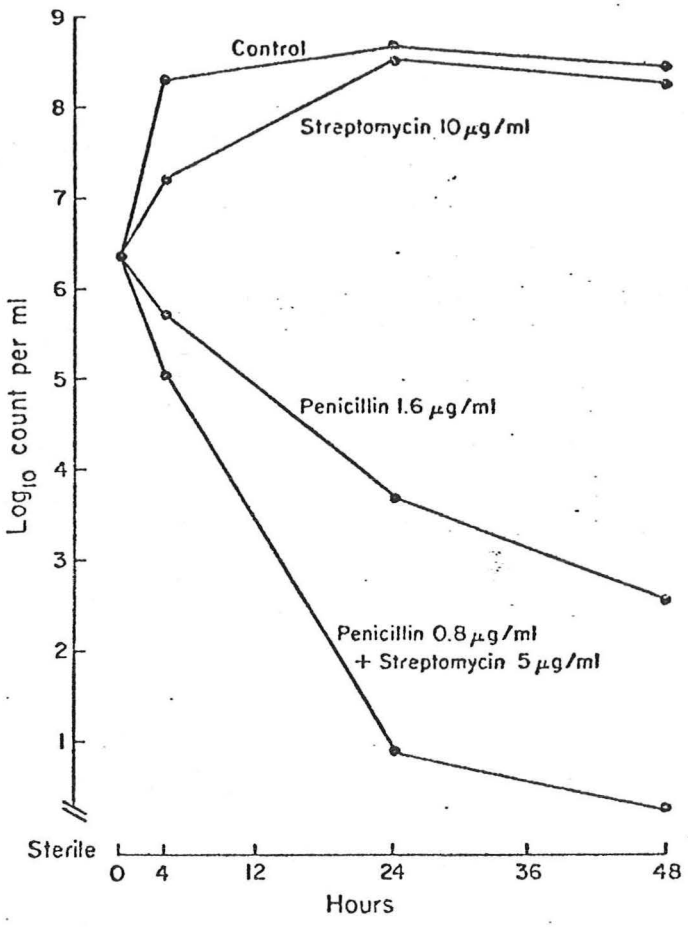


Figure 3. The geometric mean of the number of organisms recovered in synergism studies with 48 strains of viridans streptococci isolated from endocarditis patients between 1944 and 1947 and between 1967 and 1971.

This figure shows a growth curve of viridans streptococci similar to one shown previously for comparison to the enterococcus studies I will be showing later. It shows that streptomycin has little action on the organism, that penicillin decreases the population, but does not bring the curve to zero and that penicillin and streptomycin together have a more bactericidal effect. It goes without saying that although penicillin action on viridans streptococci, such as shown here, is not completely bactericidal, at least not sterilizing, a study such as this would scarcelyconvince anyone that penicillin is not valuable in the treatment of bacterial endocarditis due to viridans streptococci.

In 1970 Standiford and his associates (99) noted in conducting experiments of this sort with enterococci that although all strains were streptomycin

resistant, they fell into two groups. Approximately 60% of strains were inhibited by 2000 micrograms per ml. of streptomycin or less and the remaining 40% were more highly resistant, in many cases growing in 50,000 micrograms per ml. They also noted that on the less resistant strains, penicillin and streptomycin were "synergistic" in vitro but not so on the highly resistant strains. Numerous other studies have confirmed this work. (90)

Weinberg, Moellering and others (73,125) have studied the mechanism of antibiotic synergism against enterococci and have concluded that penicillin, like other drugs which inhibit cell wall synthesis, produces synergism against enterococci when combined with one of several aminoglycoside antibiotics. They observed that moderately high level resistance is observed in many naturally occurring strains of enterococci. In addition, very high level resistance is found in some. The mechanism for the resistance was characterized and thought to lie at the ribosomal level. Ribosomes from organisms with moderately high level streptomycin resistance (by the usual tests) were sensitive to streptomycin in vitro. This suggested that the type of resistance observed is caused by failure of streptomycin to reach the ribosomes and that in the combined action of penicillin and streptomycin, penicillin action on the cell wall permits the entrance of streptomycin. A very high level of resistance, on the other hand, appeared to be due to ribosomally mediated streptomycin resistance. It was also observed by these investigators that the failure to sterilize cultures of the high level resistance organisms did not occur when the aminoglycoside gentamicin was substituted for streptomycin.

Observations related to this in experimental endocarditis have been made by Carrizosa and Kaye. (12)

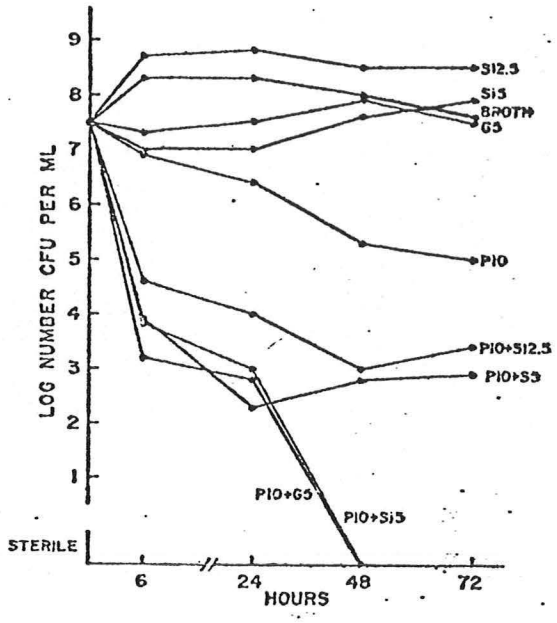


Fig. 1. Log_{10} number CFU per milliliter of enterococcus strain 1 incubated in broth, 10 μg per milliliter of penicillin G (P10), 10 μg per milliliter of penicillin G plus 12.5 or 5 μg per milliliter of streptomycin (P10 + S12.5 or P10 + S5), 10 μg per milliliter of penicillin G plus 5 μg per milliliter of gentamicin (P10 + G5), 10 μg per milliliter of penicillin G plus 5 μg per milliliter of sisomicin (P10 + Si5), 12.5 μg per milliliter of streptomycin (S12.5), 5 μg per milliliter of gentamicin (G5), and 5 μg per milliliter sisomicin (Si5).

This is a representative in vitro growth curve from their studies. Note that penicillin (in the center curve) does not have a profound effect on this particular enterococcus. The next two curves below are those of penicillin and streptomycin and you will note that these curves represent a fall in population from approximately 4×10^7 organisms down to 1×10^3 in 72 hours. The sterilizing curves noted at the bottom are penicillin and gentamicin and penicillin and sisomicin. This is the strain of organisms referred to as Strain 1, which is of moderate resistance to streptomycin.

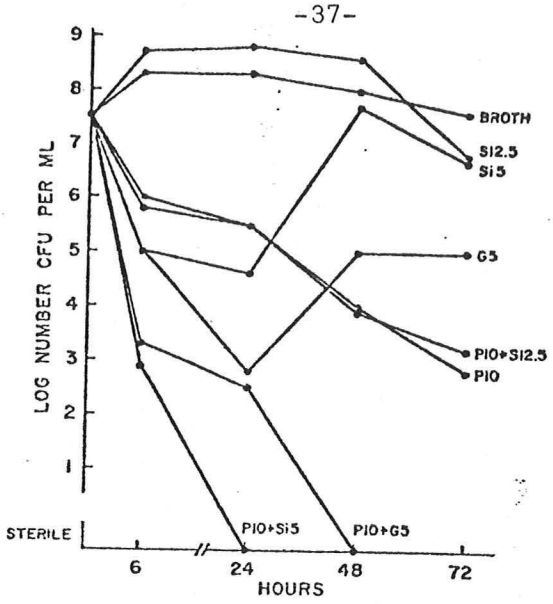
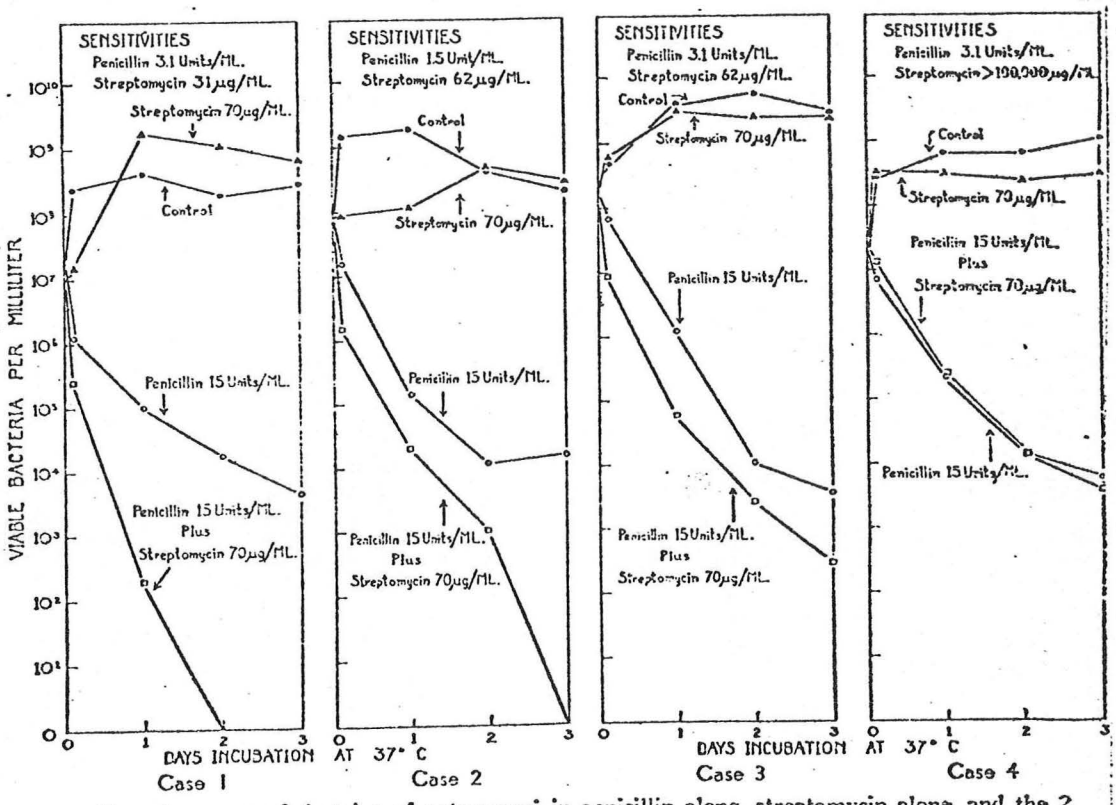


Fig. 2. Log_{10} number CFU per milliliter of enterococcus strain 2 incubated in broth, 10 μg per milliliter of penicillin G (P10), 10 μg per milliliter of penicillin G plus 12.5 per milliliter of streptomycin (P10 + S12.5), 10 μg per milliliter of penicillin G plus 5 μg per milliliter of gentamicin (P10 + G5), 10 μg per milliliter of penicillin G plus 5 μg per milliliter of sisomicin (P10 + Si5), 12.5 μg per milliliter of streptomycin (S12.5), 5 μg per milliliter of gentamicin (G5) and 5 μg per milliliter of sisomicin (Si5).

This figure shows the in vitro effect of these drugs on Strain 2, which was of high resistance to streptomycin (greater than 7,500 micrograms/ml.) These curves seem virtually identical to the previous set. Note particularly that penicillin and streptomycin lower the bacterial population in 72 hours from 4×10^7 down to 1×10^3. Thus, if these curves provided predictive information, one would anticipate that penicillin and gentamicin would be superior in both cases. When these strains are tested in animals, however, significant differences were observed between penicillin and streptomycin when compared to penicillin and gentamicin only on Strain 2, the latter being significantly better in the early treatment phase in reducing the population of organisms in the vegetations. These studies taken together with other similar studies have led to the recommendation that penicillin and gentamicin constitutes preferred therapy in enterococcal endocarditis. (12,56,113) It seems logical to assume, however, that if 40% of cases of enterococcal endocarditis cases could not be treated with penicillin and streptomycin because of lack of synergism, many failures would have been

reported since 1951. Although there may be others, I have been able to locate in the literature only three clear-cut failures of penicillin-streptomycin therapy. (Ref. 36,case 29; ref. 37,case 30, ref. 7) Two of these were successfully retreated with the same therapy, i.e. penicillin and streptomycin. I have also had one failure, but in this particular case the enterococcus did not exhibit high level streptomycin resistance. To extrapolate from this type of in vitro and animal data to the conclusion that the preferred therapy for enterococcal endocarditis demands long term administration of a drug such as gentamicin which is clearly much more nephrotoxic than streptomycin, (4) at the same time ignoring clinical results to date, seem unjustified. Further, data such as presented by Carrizosa and Kaye, in my opinion, clearly demonstrate that the in vitro studies are not predictive even of what will happen in experimental endocarditis. At least one case has been described in which organisms of a high level of streptomycin resistance have been successfully treated with penicillin and streptomycin. (105)



Growth curves of 4 stains of enterococci in penicillin alone, streptomycin alone, and the 2 drugs together

In Case 4, the last set of curves on the right, the enterococcus grew in 100,000 micrograms of streptomycin and no in vitro synergism was noted, yet the patient was cured with the two drugs. More evidence bearing on this is obviously needed.

PROPHYLAXIS

The administration of antimicrobial drugs to individuals with valvular heart disease or congenital heart disease in situations in which bacteremia is thought to be likely is a common practice. It is safe to say that every textbook and every article which deals with this question recommends prophylaxis. At the same time it must be recognized that although this is testimony to the fact that physicians believe the practice to be effective, there is clearly no evidence to prove antibiotics in fact prevent bacterial endocarditis in humans. The most commonly considered situation has to do with dental procedures and even here the risk of bacterial endocarditis is really not known. It seems even too small to permit a practical controlled study. Oddly enough, even in the field of cardiac surgery which would seem an area in which it is possible to get information, evidence is still lacking. Nonethless, accepting this practice as inevitable, various recommendations have been made as to the appropriate procedures. The following are recommendations of the American Heart Association.

Table 3. Regimens recommended by American Heart Association for prophylaxis for dental procedures

Penicillin

IM:
600,000 units of procaine penicillin G mixed with 200,000 units of crystalline penicillin G 1 hour prior to procedure and once daily for 2 days following procedure.

OR

Oral:
500 mg penicillin V or phenethicillin 1 hour prior to procedure and then 250 mg every 6 hours for remainder of that day and for 2 days following procedure.

OR

Oral:
1,200,000 units of penicillin G 1 hour prior to procedure and then 600,000 units every 6 hours for remainder of that day and for 2 days following procedure.

In patients allergic to penicillin or receiving continual oral penicillin for prophylaxis against rheumatic fever, who may harbor penicillin-resistant viridans-type streptococci.
Oral:
500 mg of erythromycin in adults (20 mg/kg in small children) 1½ to 2 hours before procedure and then 250 mg every 6 hours (10 mg/kg in small children) for remainder of that day and for 2 days following procedure.

Table 4. Regimens recommended by American Heart Association for prophylaxis for gastrointestinal and genitourinary tract surgery and instrumentation

For most patients:

600,000 units of procaine penicillin G mixed with 200,000 units of crystalline penicillin G IM 1 hour prior to procedure and once daily for 2 days following procedure plus streptomycin, 1–2 g IM, 1 hour prior to procedure and once daily for 2 days following procedure.
In children, daily dose of streptomycin is 40 mg/kg (not to exceed 1 g/24 hours).

OR

25–50 mg/kg ampicillin orally or IV 1 hour before procedure and then 25 mg/kg every 6 hours for that day and for next 2 days plus streptomycin as above.

For patients allergic to penicillin:

Erythromycin as in Table 3 plus streptomycin as above.

OR

Vancomycin, 0.5–1.0 g IV (20 mg/kg in children) 1 hour prior to procedure and then 0.5 g IV (10 mg/kg in children) every 6 hours for 72 hours plus streptomycin as above.

It seems reasonable to continue to direct our major concern towards the organisms in the mouth and those related to various dental procedures, mainly viridans streptococci. Close examination of all of the various possibilities one has to deal with tends to lead to considerable confusion.

For example, Kaye in his book lists a number of studies having to do with bacteremia associated with various procedures.(56, p. 248) The frequency after various dental procedures has varied from 0 to 92%, with an average around 40%. Interestingly enough, the frequency before the procedure was done ranged as high 11%. Everett and Hirschmann (32) have reviewed the literature in detail concerning the occurrence of bacteremia after various procedures.

BACTEREMIA AFTER VARIOUS PROCEDURES
(Everett + Hirschmann 1977)

Procedure	% Positive	Procedure	% Positive
Dental extractions	30-85	Sigmoidoscopy	0-9.5
Brushing teeth	20-24	Liver biopsy	2.9-13.5
Oral irrigation device	30-50	Barium enema	11.4
Nasotracheal intubation	16	TUR	10-57

I have constructed this table from their data. It will be noted that in the studies quoted the frequency of positive cultures after dental extractions varied from 30-85%. Brushing the teeth is also not without hazard as is the use of oral irrigation devices. Nasotracheal intubation is occasionally followed by bacteremia. Sigmoidoscopy, liver biopsy, barium enema and transurethral resection also have significant frequency of bacteremia. The organisms isolated under these circumstances are quite variable and many of the organisms are not those which generally cause bacterial endocarditis.

As previously mentioned, the major concern lies in the procedures related to the teeth. On the basis of the work on experimental endocarditis, many of the recommendations at the present time are including larger doses of penicillin and the administration of an aminoglycoside. In patients

allergic to penicillin, the use of vancomycin is recommended, rather than erythromycin or tetracycline which has been the common practice. Kaye lists also certain specific recommendations for prophylaxis against enterococci.

Table 5. Author's recommendations for enterococcal endocarditis prophylaxis (adult doses)

Regimen of choice:

Aqueous penicillin G 20,000,000 units IV daily with streptomycin, 1 g IM every 12 hours or with gentamicin, 1.7 mg/kg IM every 8 hours, starting 1 hour before procedure and continuing for 72 hours.

In patients allergic to penicillin:

Vancomycin, 0.5 g IV every 6 hours with streptomycin, 1 g IM every 12 hours or with gentamicin, 1.7 mg/kg IM every 8 hours, starting 1 hour before procedure and continuing for 72 hours.

If oral therapy must be used:

Ampicillin, 50 mg/kg plus 0.5 g of probenecid, 1 hour before procedure and then 25 mg/kg ampicillin plus 0.5 g of probenecid every 6 hours, continuing for 72 hours. Streptomycin, 1 g IM every 12 hours or gentamicin, 1.7 mg/kg IM every 8 hours should also be given starting 1 hour before procedure and continuing for 72 hours.

Similar recommendations are also made by Durack (23) who has been in the forefront of investigations on bacterial endocarditis. His recommendations are as follows:

Dental manipulations: Benzyl penicillin, 2 million units plus procaine penicillin, 600,000 units, plus streptomycin, 1 gram I.M. before the procedure.

Alternative: Vancomycin, 1 gram I.V., 5 minutes before the procedure.

Urethral, gynecological and other abdominal procedures: Ampicillin, 1 gram and gentamicin, 80 mgs. I.M. thirty minutes before the procedure, both repeated 8 and 16 hours later.

Alternative: Cefazolin, 1 gram and gentamicin, 80 mgs. I.M. thirty minutes before the procedure, both repeated 8 and 16 hours later.

Very firm recommendations on the "proper" prophylaxis which should be observed are difficult for the following reasons: First, there are so many different everyday situations in which patients are at risk. Second, as we have discussed, there is a high percentage of cases now occurring on normal valves. Third, in addition to the usual valvular and congenital disease, the very high frequency of atherosclerotic disease in the older individuals adds a significant population at risk, probably equivalent to the people with the more commonly recognized valvular disease. Fourth, the knowledge that the click murmur syndrome is associated with infective endocarditis adds an additional highly significant number of people at risk. An editorial in the Lancet entitled "Prophylaxis of Bacterial Endocarditis: Faith, Hope and Charitable Interpretations" discusses this problem in detail. (29) The concluding paragraph of this editorial expresses an attitude which is rather fatalistic but probably quite realistic. "A review of the organisms at present responsible for endocarditis, and of the antibiotics and antibiotic combinations necessary to extinguish them in vitro, might make it possible to define on reasonable grounds a small number of regimens appropriate to particular classes of patients. If that proves impossible, the logical step would be to base prophylaxis on preliminary antibiotic sensitivity tests but also on preliminary selection of totally bactericidal agents or combinations - a daunting prospect indeed considering that the risk involved is a fraction of an undefined risk, the magnitude of which is never likely to be specified, beyond good reason to believe that it is small."

NEWER DRUGS

In considering the effectiveness of newer antibiotics, four observations must be kept in mind. 1) A clear distinction must be made between the failures due to inadequacy of antimicrobial therapy, and failures due to other causes; for example, heart failure and major emboli. This is not to say they are totally unrelated, but for example, one doesn't condemn the efficacy of penicillin in a patient with infective endocarditis due to Streptococcus viridans if the patient suffers congestive heart failure due to valve destruction while under therapy. If the same event occurs in a patient under treatment with less conventional therapy, it may be interpreted as drug failure. 2) A number of drugs which will cure some cases of infective endocarditis (for example tetracycline) cannot be recommended because the percentage of cures is known to be low. It is, therefore, important in order to make a real decision that we need to know percentages of cures and frequently, with the newer drugs, we do not know this. 3) In contrast to this, in certain situations, for example with staphylococcal endocarditis, no drug really gives as favorable results as one can obtain in Streptococcus viridans infections. Under these circumstances one must be very cautious about condemning a drug if failures occur. 4) It must be recalled that many cases have been reported in which the patient is retreated after a relapse with the same therapy, ineffectual the first time, effectual the second. Thus, if relapse occurs with one drug, then the drug is changed and the second drug is successful, this does not necessarily mean that the second drug is superior.

Trimethoprim-sulfamethoxazole: This drug combination has been tested in a few cases and has been found to be ineffectual. (96)

Cephalosporin compounds: These drugs have been found useful in the treatment of endocarditis due to a number of microorganisms, notably viridans streptococci, other penicillin sensitive streptococci, and staphylococci. They are clearly not of value in the treatment of enterococcal disease. (84,85,86,114) These compounds would generally appear to be the drugs of choice in viridans endocarditis in patients who are hypersensitive to penicillin, provided the hypersensitivity is not severe or provided that adequate pre-testing occurs before full doses of the drugs are given. Whether or not all of the cephalosporin compounds will be equally effective remains to be proven. Although favorable results are reported in staphylococcal disease, some unsuccessful cases have been reported with cefazolin and a final opinion must await further experience. (11)

Vancomycin: This drug has been known for years to be useful in the treatment of Staphylococcal endocarditis. (59,66) Friedberg and his associates (35) first reported the successful use of vancomycin in patients with viridans and enterococcal disease. Subsequently, both successes and failures have been reported in the case of enterococcal disease. Here again, the experience with in vitro studies and with experimental endocarditis suggests that there may be advantages in adding an aminoglycoside when vancomycin is used in the treatment of enterococcal disease.

Carbenicillin and gentamicin: These drugs would appear to be first line drugs in the treatment of patients infected with gram negative rods, such as Serratia and Pseudomonas, provided in vitro sensitivity obtains. The nature of these infections is such that any currently available antimicrobial therapy

may be inadequate and the possibility of surgery needs to be kept in mind.

Clindamycin and lincomycin: These have been reported as successful therapy in the treatment of viridans and staphylococcal disease. The problem is the same here as with some of the other drugs mentioned, namely that the percentage of cures is not known.

Amphotericin B and flucytosine: These have been previously discussed with relation to the treatment of Candida endocarditis. As with endocarditis due to gram negative rods, the outlook is very serious, perhaps totally dismal in patients treated with antifungal drugs alone, and it would appear that surgery is virtually always indicated once the diagnosis becomes established.

Experience with other newer drugs is so limited that one can make no statements about them. Presumably, tobramycin and amikacin will be in the same category as gentamicin. Likewise, ticarcillin is likely to prove similar to carbenicillin. Also, we have not mentioned any of the newer penicillinase resistant penicillins, but their usefulness presumably is essentially the same as methicillin.

MANAGEMENT OF COMPLICATIONS

The development of the splenic abscess and splenic rupture in infective endocarditis has been the subject of two recent reports. (15a,109) The major problem here lies in diagnosis of these two disorders. Splenic infarcts are so common in infective endocarditis, and splenic abscesses and splenic rupture so uncommon, that the occurrence of left upper quadrant pain and tenderness is usually ascribed simply to another splenic infarct. The fact that abscess and rupture can occur must be kept in mind as their surgical management is relatively simple if the diagnosis is correctly made.

Finally, a major role for the surgeon in the treatment of infective endocarditis has emerged within recent years. It is not proposed to discuss this in great detail, but simply to summarize what I believe to be the current situation.

Damage to heart valves due to infective endocarditis is now the major cause of death in this disease. Congestive heart failure, brought about by valve destruction can be estimated conservatively as the cause of death in at least 50% of the deaths now occurring. The most common valve involved is the aortic valve. It has become clear that if congestive heart failure supervenes in a patient under therapy for infective endocarditis, and if it is not very responsive to ordinary medical measures, serious consideration must be given to valve surgery at that time. Newer diagnostic measures may be of value in the assessment of the need for surgery (68) and it cannot be overemphasized that the responsiveness of heart failure to medical measures may be very limited. It has also become evident that although operation on the valves in a patient with active infection carries a significant risk, the results have been surprisingly good, and many of the fears which have been expressed in the past have not been realized. Contrasted with the dismal alternative of attempting to treat these patients with medical means alone, the conclusion can only be that an aggressive approach to valve surgery in these patients is mandatory. (52a,72,77,101,119)

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