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PREFACE

The Editorial Committee and editors wish to express deep gratitude to our authors, who so willingly have shared their funds of knowledge with the readers of *Annual Review of Medicine*. We also wish to thank the subscribers who gave constructive criticism, and we take pleasure in the wide acceptance of this *Review* by those in search of authoritative surveys of medical progress. The editors gratefully acknowledge, too, the valuable aid of Miss Beryl Daniel, Editorial Assistant.

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INFECTIOUS DISEASES (BACTERIAL)

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Introduction

In recent years the interest of many investigators has gradually shifted toward the isolation, identification, and understanding of the causative agents of diseases resulting from microorganisms smaller than bacteria. Nevertheless, many fundamental and clinical problems associated with bacterial infections remain unsolved. While there is some difference of opinion as to whether staphylococci actually produce more serious infections than previously, it is generally agreed that infections caused by the staphylococcus continue to be a difficult therapeutic challenge. Evidences of bacterial infections of the kidney are found in approximately one-third of patients coming to autopsy. Pyelonephritis is, in all probability, the most common serious disease today for which there is the greatest immediate potential for prevention and treatment. The mortality rates of pneumococcal meningitis and tetanus remain high——to mention a few of the problems. It is the purpose of this review to summarize briefly some of the contributions made during the year ending July 1, 1957, to the understanding of the pathogenesis and management of bacterial infections.

Staphylococcal Infection

A conference on staphylococcal infections was held at the New York Academy of Science in February of 1956. The papers presented at this conference have been published in the *Annals of the New York Academy of Science* (1). Excellent reviews of the clinical aspects of the problem were given by McDermott (2), Spink (3), Finland & Jones (4), Knight *et al.* (5), and Collins *et al.* (6). Subsequently, an excellent discussion of the subject has been published by Rogers (7).

Staphylococcal infections continue to be a serious problem in hospitalized patients. It seems most likely that these infections have not actually increased in frequency but that there is an increase in the number of susceptible patients in hospitals. Among these patients infections are often more severe. At any rate, staphylococcal infections contracted by patients after hospital admission are likely to be more difficult to treat because of the elimination of the antibiotic-sensitive strains by the widespread use of these drugs within the hospital. The meager success in handling staphylococcal septicemia is illustrated by the experience at the Cincinnati General Hospital (8).

During the past 15 years, 55 cases of established blood stream infection were seen, 35 of which had acute bacterial endocarditis. Thirty-nine of the 55 patients died. During the seven-year interval between 1940 and 1947 when the sulfonamides, penicillin, and streptomycin were used, 83 per cent of the patients died, and since 1948, 62 per cent have died. Before 1948 87 per cent of the patients with endocarditis died and since 1948, 60 per cent died. Acute endocarditis is one of the most serious forms of staphylococcal infection and the presence of meningitis, cerebritis, and petechial hemorrhages of the skin almost always means the development of this complication. Successful management depends on prolonged high dose chemotherapy guided by *in vitro* antibiotic testing. Levin (9) reported an outbreak of staphylococcal infection occurring on the Surgical Service of Manchester, New Hampshire, Veterans Hospital. From December of 1955 through February of 1956 there were 17 cases of staphylococcal infection. These included three cases of pyogenic parotitis with one death. Many authors (3, 9, 10) have emphasized the need for elimination of cross contamination from patient to patient, aseptic techniques in handling wound dressings, and elimination of hospital carriers. Studies of the incidence of staphylococcal carriers in most hospitals have revealed the number to be quite high. Loh & Street (11) reported that among 100 hospital personnel who worked on a maternity ward of a 304-bed community hospital, 34 per cent were found to be staphylococcal carriers; 19 per cent were nasal carriers, 6 per cent pharyngeal, and nine per cent nasopharyngeal. Antibiotic sensitivity studies of the 43 strains of staphylococci isolated revealed that nine were resistant to penicillin, seven to oxytetracycline, seven to tetracycline, six to streptomycin, none to erythromycin and chloramphenicol. In contrast to this experience, most other studies have revealed a higher incidence of penicillin, tetracycline, and streptomycin resistance among strains isolated from hospital patients and personnel.

A report by Hartmann & Angevine (12) on 17 cases of pseudomembranous colitis, complicating prolonged antibiotic therapy, revealed that *Staphylococcus aureus* was isolated in some cases but absent in others. This is consistent with the opinion of others (13) that the staphylococcus is just one form of superimposed infection of the bowel but that other forms of pseudomembranous colitis occur.

Because of the incidence of strains of staphylococci resistant to the usually administered antibiotics, the search has continued for the agents active against these resistant strains. Among the antibiotics recently studied are included novobiocin, vancomycin, and ristocetin. Rutenburg, Shapiro & Schweinburg (14) reported on the use of novobiocin in the treatment of surgical infections caused by staphylococci and other Gram-positive bacteria. Most strains were inhibited by concentrations less than 6.25 μg./ml., but 2 out of 40 were resistant to concentrations greater than 50 μg./ml. The experience in the treatment of staphylococcal infections was generally good at a dosage of 250 mg. every 6 hr. Two of the 90 patients

had mild gastrointestinal side effects. There have been reports indicating a higher incidence of skin rashes in association with novobiocin therapy if doses in a range of 2 to 3 gm. daily are given.

In experimentally produced staphylococcal infections in mice, Smith (15) observed certain similarities to human infections. In experimental infections the organisms were found to survive best in the lungs and kidneys. This corresponded with human autopsy findings in 22 autopsied patients. In mice the virulence of the staphylococci was related to their ability to multiply in the mouse kidney, and in human infection the prognosis was related to the formations of abscesses in the kidney parenchyma. Further studies of infections in mice by Rogers & Melly (16) have shown that virtually all of the staphylococci in the blood stream are found within the circulating polymorphonuclear leukocytes within 10 to 40 min. after injection of the culture. There is an initial marked drop in the granulocytes in the circulating blood but by the end of 40 min. they return to the circulation in large numbers. Apparently trapping occurs initially in the pulmonary vascular bed and less constantly in the splanchnic viscera. These findings suggest the staphylococci are phagocytized by the polymorphonuclear leukocytes temporarily sequestered in the lungs and splanchnic viscera. It appears that the same sequestered polymorphonuclear leukocytes containing viable staphylococci subsequently return to the circulation. Such intraleukocytic organisms are believed to play a role in the maintenance of the bacteremia. Similar studies using *Escherichia coli* have revealed that there was a prolonged granulocytopenia following the injection of this organism and the bacteria were rapidly killed following ingestion by the polymorphonuclear leukocytes (17).

In an attempt to avoid some of the errors inherent in the production of experimental staphylococcal infections in animals, Elek (18) produced infections in the skin of man. He found that there was no significant difference in the virulence of known pyogenic strains and those from nasal carriers as measured by pus formation. He also confirmed the previous observation that the presence of foreign bodies interferes with the local defense against staphylococcal infections. E. T. Bynoe, in commenting on this paper, quoted from the experience of Barber & Burston (19) in which there seemed to be considerable difference in the virulence of strains isolated from carriers and from abscesses. Organisms transmitted from nursery employees to babies rarely caused severe infection, but when a nurse entered the nursery with a boil on her face, several severe infections occurred. One must still take into consideration the dose of infecting organisms when evaluating virulence.

While the staphylococcus shows many interesting biologic properties, Lack (20) believes there is little evidence that these have any relationship to pathogenicity. Even the much used coagulase test is of little value in separating pathogenic and nonpathogenic strains although there is some association between coagulase production and resistance to neutrophil

lysozyme. Ekstedt (21) showed a close correlation between coagulase production and the ability of the strain to grow well in normal undiluted human serum. He felt that there was little evidence of a direct correlation between either of these properties and pathogenicity. According to Rammelkamp & Lebovitz (22), the evaluation of the role of coagulase in staphylococcal infections is further complicated by the fact that most adults have a fairly high titer of reacting factor in serum which interferes with the evaluation of the coagulase reacting factor system in human infection. They suggest that studies in children might clarify the role of this system since the titer of reacting factor is rarely elevated in young age groups. Relative to this same problem Fishman & Silverman (23) isolated from the polymorphonuclear leukocytes by ultrasonic technique a substance from the mitochondrial section of the cells which has a bactericidal effect against many bacteria. As little as 0.31 μg. of nitrogen-containing material was capable of killing 2,000 cells of *Micrococcus pyogenes*. This substance was differentiated from lysozyme by its heat stability, ultraviolet spectrum and enzymatic inactivation, and in having a wider antibacterial spectrum of activity.

Wise (24) has cultured small colonies (G variants) of staphylococci from patients. These variants were more resistant to antibiotics than the parent strain. They were avirulent but remained viable in animal tissues without producing infection. When they are subcultured in nutrient broth they revert to large colonies. It is suggested that these variants may persist in human tissue during and following antibiotic therapy and serve a subsequent source of relapse or recurrent infection.

The staphylococcal enterotoxin has been purified and its properties described by Bergdoll (25). Satisfactory assay procedures have not been developed.

Bacterial Infections of the Urinary Tract

There is evidence of increasing awareness of the tremendous problem of bacterial infections of the urinary tract as manifested by the increase in number of papers appearing on various aspects of this subject during the past year. An excellent review by Derow (26) summarizes the present concepts of the pathogenesis and treatment of pyelonephritis.

The understanding of many aspects of this disease has been delayed by difficulties in the production of the disease experimentally in animals. Braude, Shapiro & Siemiensky (27, 28) reported two years ago of the production of hematogenous pyelonephritis in rats. This was done by massaging the kidney and injecting cultures of the *E. coli* intravenously. It is well known that urinary tract infections are often associated with obstruction of the ureter. Guze & Beeson (29) have attempted to elucidate the mechanism by which obstruction affects the susceptibility of the kidney to infection. The ureter in rats was ligated and *E. coli* or *Serratia marcescens* injected intravenously. During the first few hours following the injection,

approximately equal numbers of bacteria could be recovered from the kidney on the obstructed side as compared to that on the unobstructed side. After 4 hr., however, an increased number of bacteria could be demonstrated on the obstructed side, apparently the result of multiplication, and by the end of 24 hr. purulent infection was usually present. It was concluded that the increased susceptibility of the obstructed kidney to infection introduced by way of the blood stream was not attributable to an increased trapping of circulating bacteria.

A study by Kass & Schneiderman (30) demonstrated that bacteria may enter the bladder in patients having indwelling catheters, even though the interior of the catheter is not contaminated. A small amount of a culture of *S. marcescens* was applied to the periurethral epithelium of one female and two male patients with inlying catheters. Within one to three days large numbers of the test organisms were recovered from the urine of these patients. It was suggested that the entry was by way of the fluid composed of urine and exudate that usually forms around the catheter.

It is often difficult to evaluate the significance of positive urine cultures. In an attempt to shed some light on this problem, MacDonald *et al.* (31) studied the relationship between pyelonephritis and bacterial counts of the urine. Bacterial counts of bladder urine were performed in 100 unselected autopsies and these findings were correlated with the results of pathologic study of the kidneys. Forty per cent of the urine specimens obtained at autopsy by needle aspiration of the bladder contained more than 100,000 bacteria per ml., 53 per cent contained no bacteria, and 7 per cent contained between 10 and 10,000 organisms per ml. Histologic evidence of active pyelonephritis was found in 14 of the 40 patients with greater than 100,000 bacteria per ml. and occurred in only 3 of the 60 patients with no or relatively few bacteria. In three cases of acute cystitis there were more than 100,000 bacteria per ml. The organism isolated most frequently was *Aerobacter aerogenes* and the review of the cultures taken prior to death revealed little tendency of the organism to disappear with treatment. Antimicrobial therapy had been given up to at least 24 hr. before death in 60 to 70 per cent of the patients but beneficial effects of such therapy were limited. Healed pyelonephritis occurred in 18 per cent of the patients and the prevalence bore no relationship to bacteriuria. Thirty-three per cent of unselected autopsies revealed evidence of active or healed pyelonephritis. Substantial correlation between the bacteriuria, pyelonephritis, and inlying catheterizations was demonstrated. The clinical diagnosis of active infection of the genitourinary tract was not made in 70 per cent of the cases in which active pyelonephritis was demonstrated histologically. In many of these patients, extensive pyelonephritis was found at autopsy. The authors stated that pyuria, azotemia, cylindruria, and albuminuria were not reliable indices of the presence or absence of bacteriuria or pyelonephritis and they found little or no relationship between hypertensive heart disease, increased diastolic pressure, and the bacteriuria found.

Guze & Beeson (32) reported observations on the reliability and safety of bladder catheterizations for bacteriologic study of the urine. Urine cultures were taken on 13 women after careful cleansing of the genitalia and urethra just prior to undergoing gynecologic surgery. After the catheter was inserted into the urethra it was swirled in sterile saline; 2 ml. of this were cultured in thioglycollate broth and pour plates were made of the saline. There was growth in six cases: *E. coli* was isolated in four, *E. coli* and staphylococcus in one, and *A. aerogenes* in one. However, the pour plates revealed that the colony count was less than 100 per ml. in each case, suggesting that the bacteria could have been introduced by the catheter as it passed through the urethra. In 12 patients, bladder urine was obtained by needle aspiration through the bladder wall during a laparotomy. This urine was compared with specimens obtained by catheterization shortly afterward. In eight of the patients both samples showed no growth. In four, the urine from the bladder was sterile, but the catheterized urine obtained a few minutes later showed *E.* coli in three, *Pseudomonas aeruginosa* in one, and the pour plate from one patient showed only three colonies per ml. In one of the twelve patients, an acute urinary tract infection developed clinically 36 hr. after catheterization. These authors concluded that a clean voided specimen inoculated on solid media was the preferable method of obtaining a urine culture.

Studies by Berg, Weinberger & Dienes (33) suggest the possibility that pleuropneumonia-like organisms may be important in the pathogenesis of unexplained genitourinary infections. Of 88 patients with unexplained genitourinary infections, 57 had positive cultures of pleuropneumonia-like organisms. Most of the 57 symptomatic patients with positive cultures had symptoms suggestive of urethritis. Fourteen of them had arthralgias and eight of the patients had conjunctivitis.

The importance of pyelonephriits in pregnancy, often masquerading as toxemia of pregnancy, was reviewed by Finnerty (34). Of 1130 patients referred to the toxemia clinic at the District of Columbia General Hospital, 73 were found to have pyelonephritis. None of these had any urinary tract symptoms, fever, or costovertebral angle tenderness. The diagnosis was made by microscopic urinalysis and urine culture. Thirty-seven were antepartum, referred because of toxemia and 36 were postpartum, referred because of persistent albuminuria. *E. coli* was cultured in 41, *E. intermedius* in seven, *Proteus* in five, *A. aerogenes* in three, *P. aeruginosa* in three, *Micrococcus* in three, and paracolon bacteria in one.

An excellent review of the pathogenesis, course and treatment of nonobstructive pyelonephritis was reported by Brainerd & Cecil (35).

Bacterial Endotoxins

Interest has continued in the relationship between bacterial endotoxins and the production of certain physiologic changes associated with bacterial disease. Differences of opinion still exist regarding the relative importance

of the meningococcal endotoxin and insufficiency of the adrenal cortex in the production of peripheral circulatory collapse in fulminating meningococcemia. A paper by Kanter & Learner (36) reported findings in ten recently treated cases of meningococcemia with vascular collapse. Five of these patients died despite antibiotics, sulfonamides, adrenal steroids, and norepinephrine. Three died in the first 24 hr., and at autopsy all had massive adrenal hemorrhage. One died in 48 hr. with an acute myocarditis and congestive heart failure, and one died in seven days with extensive cerebral, cardiovascular, renal, and adrenal damage. Of the five who survived, two had slow convalescence because of acute myocarditis but none had evidence of chronic adrenal insufficiency as measured by urinary 17-ketosteroid excretion and by circulating eosinophil counts.

In studies of the role of epinephrine in reactions produced by endotoxins of Gram-negative bacteria, Thomas (37) produced extensive lesions of dermal hemorrhagic necrosis in rabbits by injecting epinephrine or norepinephrine into the skin within 4 hr. after intravenous administration of endotoxin. As little as 5 μg. of intradermal epinephrine and 1 μg. of intravenous endotoxin were sufficient. No lesions were produced by a combination of endotoxin with serotonin and vasopressin or ephedrine. These dermal lesions could be prevented by the pretreatment with cortisone, phenoxybenzamine (Dibenzyline), and chlorpromazine, but not by heparin or nitrogen mustard, both of which inhibit the Shwartzman phenomenon. The nitrogen mustard actually increased the size of the lesions. It was concluded that the endotoxin altered the reactivity of blood vessels to epinephrine in such a way that this hormone becomes a potent necrotizing agent. In a second paper on this subject, Zweifach, Nagler & Thomas (38) discuss the changes produced by the endotoxin in the vascular reactivity to epinephrine in the rat mesoappendix and the isolated perfused rabbit ear. Following the intravenous injection of sublethal doses of endotoxin, the terminal arterioles and venules exhibited greatly augmented and prolonged vasoconstrictor responses to epinephrine and norepinephrine. Hyper-reactivity became evident within 30 min. and persisted as long as 6 hr. After large doses, vascular hyper-reactivity to epinephrine was of briefer duration and was followed by marked hyporeactivity. With lethal doses the terminal arterioles and venules became completely refractory to epinephrine while hyper-reactivity persisted in larger arteries and veins. The end result was pooling of blood and distended capillaries and venules accompanied by the appearance of petechiae. Tolerance to endotoxin by repeated small doses eliminated this effect. It was suggested that abnormal reaction to epinephrine and norepinephrine in the tissues of the intact animal may represent the basic mechanism in the intoxicating and tissue-damaging properties of endotoxin.

The mechanism of the protective effect of chlorpromazine against the *Brucella* endotoxin was studied by Abernathy, Halberg & Spink (39). The survival time in both intact and adrenalectomized mice when challenged

with lethal doses of *Brucella* endotoxin was prolonged by treatment with chlorpromazine. This effect did not appear to be critically dependent on corticoid-stimulating, sedative, adrenolytic, antihistaminic, or hypothermic effects of the drug. Weil *et al.* (40), in an attempt to determine the role of the central nervous system in shock, injected endotoxin from *Brucella melitensis* and *E. coli* intravenously into dogs. The characteristic hemodynamic changes associated with arterial hypotension and portal hypertension were measured directly with a strain gauge manometer. Cross cerebral circulation studies showed that both dogs developed the same changes. Arterial hypotension was not prevented by chordotomy with or without vagotomy. In decapitated dogs there was also a prompt fall in arterial blood pressure with a rise of the portal venous pressure. When the entire spinal cord of cats was pithed, endotoxin still caused a profound drop of arterial pressure with a small elevation of portal venous pressure. These findings do not support the thesis that the initial manifestation of shock produced by endotoxin is a result of a direct action on the central nervous system.

On the other hand, Keene (41) reported that when *Shigella* endotoxin was injected intrathecally in the rabbit it was a thousand times as effective in producing fever as when given intravenously. The latent period was 10 to 12 min. shorter than by way of the intravenous route when the same dose was given. Animals tolerant to the intravenous dose did not demonstrate tolerance to the intrathecal dose. There was no significant leukopenia in contrast to that seen following intravenous injection.

In studying the effect of heat on exogenous and endogenous pyrogens in the serum of dogs, Petersdorf & Bennett (42) presented evidence to support the concept that endogenous pyrogen was not a product of injured tissue but represented a modification of endotoxin by plasma components. Further studies (43) by these authors on the pathogenesis of fever revealed that sterile canine peritoneal exudates containing leukocytes were capable of producing fever when injected into normal dogs but were nonpyrogenic in rabbits. The capacity of these fluids to produce fever was destroyed by heating at 90°C. and they did not produce tolerance when repeatedly injected. They were as potent in normal dogs as in dogs with acquired resistance to bacterial endotoxin. Rabbit exudates are nonpyrogenic for dogs. These findings suggest species specificity in activity of the endogenous pyrogens.

A clinical report by Ezzo & Knight (44) of 38 patients with bacterial shock revealed experiences similar to those described by others. Twenty-three of the 38 cases were caused by Gram-negative bacillary infections and 14 by Gram-positive cocci. The usual portal of entry was the genito-urinary tract. The authors were impressed by the relationship between the inflammatory reaction at the portal of entry and the severity of the bacterial shock and ultimate mortality. The use of vasopressors, antibiotics, and corticoids resulted in recovery in 13 cases. The precise value of each in a therapeutic regimen was difficult to determine.

The role of endotoxin in the susceptibility of animals to bacterial infections was studied by DuBos & Schaedler (45). Mice were injected intraperitoneally with one of the endotoxic active products, either pertussis vaccine, heat killed *Klebsiella pneumoniae,* or *Salmonella typhosa* purified lipopolysaccharide. Animals were then given intravenously virulent cultures of coagulase-positive staphylococci, organisms of bovine tuberculosis, or Friedlander's bacilli. A comparison was made of mortality rates in the control and treated groups. Mice receiving infected cultures within a few hours of endotoxin were more susceptible than normals. In contrast, those infected several days after receiving endotoxin were more resistant than normal. The same authors (46) studied changes in susceptibility to infections brought about by nutritional disturbances. In guinea pigs the intradermal injection of 2 μg. of epinephrine lowered the resistance to infection by *Pseudomonas, Proteus, E. coli, S. aureus, C. diphtheriae, Streptococcus hemolyticus,* and *Clostridium welchii,* if the bacteria were injected within 2 hr. at the same site. Mice fed deficient diets were shown to have decreased resistance to infection as manifested by increased mortality. However, they progressively recovered normal resistance while being kept on the same inadequate diet. Susceptibility seemed to increase during periods when animals were losing weight regardless of the cause of the weight loss. These changes were reversible and could occur within short periods of time. This was not thought to be correlated with the properdin level.

The injection of lipopolysaccharide in mice, on the other hand, caused a rapid rise in the resistance to infection, accompanied by a rise in properdin titer to levels of two to three times normal (47). Control animals infected with Gram-negative organisms showed progressive decline in properdin levels and ulitmately the animals died. Those treated with the lipopolysaccharide maintained a normal or increased properdin level and the infection was successfully managed.

Infections Complicating Antibiotic and Steroid Therapy

There is an increasing experience in the association of both fungal and bacterial infections seen in association with antibiotic and steroid therapy. Torack (48) reported eight cases of monilial infection, two of *Aspergillus* and three of *Mucor.* Smith & Cleve (49) describe six cases of severe infection with three deaths occurring in patients receiving steroid therapy. One had a disseminated monilial infection, one a disseminated histoplasmosis, one a staphylococcal septicemia and acute endocarditis, and two had large gluteal abscesses.

Brucellosis

Three cases of chronic localized pulmonary brucellosis were reported by Weed, Sloss & Clagett (50). There were solitary pulmonary lesions found to be caseous granulomas when surgically excised. *Brucella suis* was isolated from each of these. Additional cases of unusual forms of brucel-

losis have been reported: one in the case records of the Massachusetts General Hospital (51) in which there were localized granulomata of the spleen with focal calcifications in association with a hemolytic anemia. A similar case was reported from the Mayo Clinic by Osmuadson, Martin & Stroebel (52) of an individual who had had evidence of the disease for 14 years. Massive splenomegaly, thrombocytopenia with calcified granulomas in the spleen and liver were present. *B. suis* was cultured from this patient. Recently Spink (53) has reported a similar case.

Bacterial Endocarditis

As operations have been performed more frequently on the heart and vessels, the occurrence of postoperative endocarditis has been observed with increased frequency. A case is reported in which cardiac catheterization and mitral commissurotomy were followed by endocarditis caused by *Staphylococcus albus* which was highly resistant to penicillin (54). The patient recovered with combined erythromycin and streptomycin therapy. Geraci (55) has reported further experiences with short-term therapy of combined penicillin and streptomycin for bacterial endocarditis caused by penicillin-sensitive streptococci. He reported an additional 23 cases of a total of 46, with no treatment failures or relapses. Patients in the earlier group were given 2,000,000 units of aqueous procaine penicillin and 2 gm. of streptomycin, divided in two doses and given at 12 hr. intervals. All strains in this group except one were sensitive to 0.1 units of penicillin per ml. *in vitro,* one being sensitive to 0.2 units. In the 23 patients treated subsequently there were six strains sensitive to penicillin concentrations of between 0.1 and 0.5 units. All patients were treated for two weeks. The treatment of staphylococcal endocarditis is reviewed by Melton & Logue (56). Six cases of subacute staphylococcal endocarditis are reported with cures in all but one. The successful therapy in this group illustrates the tremendous difference in prognosis in subacute staphylococcal endocarditis as compared to acute staphylococcal endocarditis. Austrian (57) reported observations on six cases of pneumococcal endocarditis. All of these patients except one had an associated meningitis and each had evidence of rupture of the aortic valve. Four of the patients died. This and other reports suggest that rupture of the aortic valve is more commonly seen in pneumococcal and staphylococcal endocarditis than in other forms of endocarditis.

A review of the hematologic changes in endocarditis was reported by Daland *et al.* (58). They stated that there is a wide variation in the leukocyte count, but that numerous histiocytes were often seen in the circulating blood with phagocytized red blood cells. These were seen more frequently in blood taken from the ear lobe than from the finger tip. There may also be toxic granulations of the neutrophils, especially in the terminal stages of the disease. A case illustrating the central nervous system manifestions of subacute endocarditis was reported by Antel *et al.* (59). The patient