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Extracardiac Manifestations of Bacterial Endocarditis

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Bacterial endocarditis is an elusive disease that challenges clinicians' diagnostic capabilities. Because it can present with various combinations of extravalvular signs and symptoms, the underlying primary disease can go unnoticed.

A review of the various extracardiac manifestations of bacterial endocarditis suggests three main patterns by which the valvular infection can be obscured. (1) A major clinical event may be so dramatic that subtle evidence of endocarditis is overlooked. The rupture of a mycotic aneurysm may simulate a subarachnoid hemorrhage from a congenital aneurysm. (2) The symptoms of bacterial endocarditis may be constitutional complaints easily attributable to a routine, trivial illness. Symptoms of low-grade fever, myalgias, back pain and anorexia may mimic a viral syndrome. (3) Endocarditis poses a difficult diagnostic dilemma when it generates constellations of findings that are classic for other disorders. Complaints of arthritis and arthralgias accompanied by hematuria and antinuclear antibody may suggest systemic lupus erythematosus; a renal biopsy study showing diffuse proliferative glomerulonephritis may support this diagnosis. The combination of fever, petechiae, altered mental status, thrombocytopenia, azotemia and anemia may promote the diagnosis of thrombotic thrombocytopenic purpura.

When the protean guises of bacterial endocarditis create these clinical difficulties, errors in diagnosis occur and appropriate therapy is delayed. Keen awareness of the varied disease presentations will improve success in managing endocarditis by fostering rapid diagnosis and prompt therapy.

BACTERIAL ENDOCARDITIS is an elusive disease. Protean systemic manifestations and the latency of cardiac symptoms often combine to obscure the presence of valvular infection. A common error in diagnosis occurs when an extracardiac complication of endocarditis is mistaken for a separate disorder. A cutaneous vasculitis, a migratory polyarthralgia or a ruptured cerebral aneurysm may appear to be a primary disease when evidence of cardiac involvement is subtle. The consequent delay of correct evaluation decreases

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ABBREVIATIONS USED IN TEXT

ANA = antinuclear antibody
DIC = disseminated intravascular coagulation
SBE = subacute bacterial endocarditis

the probability of a successful outcome to antibiotic therapy.

This paper reviews the characteristic extracardiac manifestations of bacterial endocarditis. Emphasis is placed on the clinical complications and laboratory signs which should suggest endocarditis in difficult instances in which little direct evidence of valvular infection exists.

Immunological Manifestations

In patients with bacterial endocarditis, a polyclonal immunological response to foreign proteins develops. A number of autoantibodies and exoantibodies develop of which only 15 percent have specificity for the invading organism.[1]

There are several manifestations of this heightened immunological state. Rheumatoid factor has been found in 24 percent to 50 percent of patients with subacute bacterial endocarditis (SBE)[2-5] and can occur in titers as high as 1:5,120.[2] It tends to develop in patients with long duration of disease.[6] If endocarditis has been present for six weeks, 50 percent of patients have positive test results for rheumatoid factor, while only 6 percent have positive results if disease has been present for less than six weeks.[4] There is no correlation with type of infecting organism[5,6] or with degree of immune complex elevation.[7] Apparently, continuous antigenic exposure versus intermittent stimulation is necessary since drug abusers with staphylococcal endocarditis have a 24 percent incidence of rheumatoid factor, while only 7 percent of noninfected abusers who intermittently inject antigen were found to have measurable levels.[4] After the initiation of antibiotic therapy, titers may immediately decline and become negative in six to eight months.[4,5]

Cryoglobulinemia of the mixed type has a prevalence of 90 percent in SBE. The degree of elevation tends to parallel the course of the disease but does not prognosticate or appear to be higher in patients with nephritis.[8]

Circulating immune complexes assayed by the Raji method are found in endocarditis.[7,9] In one study, 97 percent of patients with SBE had levels greater than 12 μg per ml, while this level was found in 32 percent of patients with sepsis, 40 percent of drug addicts and 10 percent of normal controls. Levels greater than 100 μg per ml were not found in any patient without endocarditis and occurred in 35 percent of the SBE group. This degree of elevation correlated with duration of disease and extravalvular signs such as splenomegaly, arthralgia-arthritis, Roth spots, nephritis and thrombocytopenia. All patients whose cases are followed serially have a fall in immune complex levels with successful therapy. Persistent elevations may foretell treatment failure.[7]

Measurements made early in the course of endocarditis show serum complement to be variably elevated,[1] normal[2] or low[7] in patients without nephritis. However, if complement is followed serially during therapy there is generally a rise in titer and any initial depression corresponds inversely to the elevation of circulating immune complexes.[7] Patients with nephritis uniformly have total complement depression,[2,10-12] which responds to antibiotic therapy.[12]

As would be expected in endocarditis with its broad nonspecific hyperimmune state, other antibodies have been noted. Results of tests for antinuclear antibody (ANA) are positive in 8 percent to 30 percent of SBE patients, with titers as high as 1:640. Positive ANA test results revert to negative after antibiotic therapy.[1-3,9,12] Also occurring are antiheart antibody;[3] positive tests for syphilis (Venereal Disease Research Laboratory);[3] antibody against Candida albicans,[1] and several other organ-specific antibodies: smooth muscle antibody,[1-9] mitochondrial antibody,[1,9] thyroidal antibody, gastric parietal cell antibody and skeletal muscle antibody.[1]

Cutaneous Manifestations

Probably no sign of endocarditis is as widely advertised, yet is of as little value as subungual splinter hemorrhages. The specificity of this sign for endocarditis is very low. Of all patients admitted to hospital, 10 percent to 66 percent have splinter hemorrhages,[13,14] with highest incidences in patients with mitral stenosis without endocarditis[15] and in those in whom hemodialysis[16] or peritoneal dialysis is being carried out.[14] Because this finding is noted in only 12 percent of patients with SBE,[17] it provides little diagnostic value as an isolated finding. The finding is important for patients with known or suspected endocarditis in whom splinter hemorrhages develop

during in-hospital observation, thereby providing evidence for ongoing disease.[18]

Osler nodes, which occur in endocarditis, are painful nodes similar to wheals that develop most often on the pads of the fingers and toes or on the palms and soles. Always erythematous with slightly white centers, they differ from Janeway lesions in their tenderness and lack of hemorrhage. They have been reported in systemic lupus erythematosus,[19] typhoid fever, gonorrhea, marantic endocarditis, as well as acute[20] and subacute endocarditis. In the preantibiotic era, their frequency was 50 percent to 70 percent, but they now occur in 10 percent to 23 percent of cases.[18] However, when present they may be a chief complaint,[17] suggesting the diagnosis of endocarditis or allowing early identification of organisms on Gram stain.[21]

The pathogenesis of Osler nodes is not yet settled. Osler felt they were "in all probability caused by minute emboli."[22] Biopsy reports[23] showing necrotizing vasculitis of the dermal glomus with sparing of the dermal vessels, along with burgeoning evidence that many other complications of endocarditis are immune related, have led some to conclude that Osler nodes are inflammation from immune complexes settling into tissue.[9] However, these biopsy specimens were generally taken after the lesions had been present for ten days. When earlier specimens are examined, microabscesses have been seen[24] and organisms cultured[20,21,24] or observed on Gram stain.[21,24] These results suggest that the perivasculitis may be a local response to a septic embolus rather than a reaction to a diffuse immunological event. This view fits the observations that Osler nodes occur preferentially in the distal circulation and that they are rare compared with other immunological complications such as nephritis.

Petechiae remain one of the most common signs of endocarditis; they occurred in 85 percent of patients in the preantibiotic era and occur in 19 percent to 50 percent now.[18] They do not blanche, and they occur most commonly around the clavicle, lower neck, conjunctivae, and hard or soft palate. They appear in waves and crops, lasting a few days before fading into brown spots.

In endocarditis, petechiae rarely progress to generalized purpura.[25-30] In staphylococcal endocarditis, purpuric lesions may progress into cutaneous gangrene[28,29] or may be pustular, with organisms present on Gram stain.[29,30] Pathological sections show intravascular thrombosis, focal necrosis of vessel walls, extravasation of erythrocytes[26] and IgM deposition in the dermoepidermal junction.[31] Platelet counts may be normal[25] or depressed,[29,30] and clotting studies either give normal findings[25] or results consistent with disseminated intravascular thrombosis.[29,32] The clinical pattern of acute meningococcemia[29] or leukocytoclastic vasculitis[27] may be mimicked when endocarditis presents with generalized purpura.

Nail clubbing has long been a hallmark of subacute endocarditis; it occurred in 76 percent of cases in older series and occurs in 12 percent to 52 percent in the antibiotic era.[18] Rarely, it can be associated with hypertrophic osteoarthropathy.[33]

Splenic Manifestations

Splenomegaly occurs in 23 percent to 57 percent of endocarditis patients.[18] Spleens as large as 1,400 grams[34] are sometimes the major mode of presentation, suggesting an underlying lymphoreticular disease. Splenic infarctions resulting from arterial emboli are the greatest cause of splenomegaly[24] and are found in 40 percent to 60 percent of autopsies done in cases of endocarditis.[18,35,36] Splenic infarcts are seldom symptomatic; but they can generate severe left upper quadrant pain, local rebound, the Kehr sign, pleuritic pain and a friction rub.[34] The pain of splenic infarction may be the presenting complaint in 5 percent of patients and can lead to a diagnosis of pulmonary embolus, pneumonia or a primary intraabdominal event. A spleen scan may give positive results, showing a defect if the infarct is large enough.[37]

Although the infarcts are due to infected emboli, the low virulence of the organisms usually results in a nonsuppurative lesion; splenic abscesses rarely develop. In the preantibiotic era, 10 percent of patients who died of endocarditis had suppurative foci in the spleen; since the introduction of antibiotics, only a few cases have been reported.[38-40]

Splenic rupture rarely occurs in endocarditis; but, when present, it is a particularly lethal complication. Rupture may be the first manifestation of disease, or it may occur after the endocarditis has been bacteriologically cured.[36]

Pulmonary Manifestations

X-ray studies of the chest in cases of left-sided endocarditis are generally not revealing in the

absence of congestive heart failure. Pulmonary manifestations are due to right-sided cardiac infection or left-sided involvement with a left-to-right shunt;[41,42] most often they occur in intravenous drug abusers or in immunosuppressed patients.[41] Tricuspid infection is common in these persons; with or without other valve involvement, endocarditis occurs on the tricuspid valve in 72 percent of heroin addicts with endocarditis, and pulmonary disease may be the major presenting feature in 66 percent.[41,43] The clinical features are fairly uniform: There is usually no previous heart disease and minimal evidence for a cardiac disorder; pulmonary dysfunction is the apparent primary problem with chest pain, cough and shortness of breath as the most common chief complaints.[41] An x-ray film of the chest may show pneumonia demonstrated by cavitary or multiple alveolar infiltrates, pulmonary emboli in 10 percent to 38 percent,[43] empyema, pneumothorax, lung abscess, pleural effusions and pulmonary artery mycotic aneurysms. The valvular infection may go unnoticed because a cardiac murmur is absent in 45 percent of patients if pulmonary complications occur.[43] Staphylococcus aureus is the most common organism in this setting,[43-45] and mortality is low with early diagnosis and aggressive therapy.

Neurological Manifestations

Neurological complications of bacterial endocarditis present diversely and closely mimic primary central nervous system processes. Between 15 percent and 50 percent of patients will have neurological complaints during the course of disease,[34,46-48] and these complaints will be the major presenting problems in 6 percent to 28 percent.[47] The incidence of neurological manifestations is the same in subacute and acute endocarditis, and the frequency has not decreased with the development of antibiotics.[47,48] Mortality is only marginally increased in groups of patients in whom general neurological complaints develop,[46] but it is significantly higher if a major complication such as a stroke, delirium or coma occurs.[17]

Major emboli to the central nervous system occur in 30 percent to 50 percent of patients with subacute endocarditis;[18,35,48] and, conversely, 3 percent of all emboli to the head originate in infected valves.[18] The emboli most commonly lodge in the middle cerebral artery, producing hemiplegia and parietal signs.[18,46] However, essentially any arterial watershed is in jeopardy, and any constellation of ischemic neurological signs can develop. Emboli to the spinal cord are rare but can produce girdle pain or paraplegia.[18]

Embolic episodes are not limited to the period of active valve inflammation and can be manifest months to years after a bacteriological cure.[18,41,47,49] Cates and Christie observed an 11 percent incidence of cerebral emboli with an 80 percent early mortality in patients without atrial fibrillation occurring one to 70 days after cessation of antibiotic therapy.[49] The higher mortality of late emboli as compared with early emboli suggests that healed vegetations present a greater threat since they are fibrosed and calcified with resultant emboli that are larger and less likely to break up in the intracranial arterial circulation than are the friable particles embolized during active valvular inflammation. Valve replacement or debridement[5] is warranted for recurrent emboli.

Occult endocarditis may present as aseptic or purulent meningitis. Aseptic meningitis is much more common than the purulent form in subacute endocarditis.[18,47,48] The resulting meningoencephalitis may be severe, with nuchal rigidity and an acute brain syndrome. Analysis of cerebrospinal fluid commonly shows no organisms on smear or culture, fewer than 500 leukocytes per cu mm most of which are mononuclear, elevated protein value and normal glucose value.[48] The meningeal findings usually are transient and resolve completely whether or not the patient receives antibiotics.

Acute suppurative meningitis is a complication of acute, usually staphylococcal,[46] endocarditis and is the most common neurological presentation of endocarditis with this organism.[2] When S. aureus is involved, the cerebrospinal fluid findings are often nonspecific: The leukocyte count is generally less than 1,000 per cu mm with a predominance of polymorphonuclear cells; the protein value is elevated; the glucose value is usually normal, and cultures or smears are positive in only 20 percent of instances.[51]

Brain abscesses are rare in SBE (1 percent of cases) but are found in 24 percent of cases of acute endocarditis, usually as small multiple abscesses.[47,48] They may present as sterile meningitis, intracranial mass lesions or a toxic encephalopathy.[47] Generally, drainage procedures are ineffective because the lesions are small and are often multiple.[18,35,48]

Intracranial mycotic aneurysms complicate bacterial endocarditis in 2 percent to 18 percent of

instances[17,18,47,52] and are more frequent with noninvasive organisms than with S. aureus which usually promotes abscess formation.[18,48] However, mycotic aneurysms are sufficiently common in acute endocarditis that diagnostic procedures are warranted if the clinical findings are even slightly suggestive of an aneurysm.[17,53] The actual incidence in all forms of endocarditis may be higher; cerebral angiography is not done in all patients, and many may remain asymptomatic. Of all intracranial aneurysms in general patient populations, 2.5 percent to 4 percent are mycotic.[54] They usually occur singly, but they can be multiple; they are most frequently found along the middle cerebral artery, although any artery is subject to them.[18,47] They differ from congenital aneurysms by being more peripheral beyond the first bifurcation and are less often in the anterior circulation,[18] but exceptions do occur.[55]

The importance of mycotic aneurysms is greater than their frequency would suggest; often the first sign of their existence is a fatal intracranial hemorrhage. Rupture, which carries a 60 percent to 90 percent mortality,[47] may be prevented in some cases with early diagnosis, close observation and surgical intervention when possible. The unpredictability of outcome is pronounced: fatal rupture may occur one to 22 months after the cessation of administration of antibiotics and bacteriological cure.[17,54]

Premorbid symptoms of a mycotic aneurysm do occur, but more frequently the aneurysm ruptures unexpectedly. The symptoms of impending rupture are the same as those seen with cerebral aneurysms resulting from other causes.

Once established, aneurysms have variable natural histories. They may rupture early or late, may persist unchanged except for wall calcifications, may thrombose and decrease in size or may resolve with complete disappearance in possibly half of the cases.[56-58]

Four-vessel cerebral angiography is required to show the existence of a mycotic aneurysm. There are no reports of success in utilizing computerized tomography. Because of the potential lethality, an aggressive approach should be adopted for prompt diagnosis in certain situations. Any patient with endocarditis in whom there is sterile meningitis with focal neurological signs or unilateral headache, or both[59] or a patient with endocarditis and a subarachnoid hemorrhage[55] should have an angiographic study. Once the aneurysm is diagnosed in an initial arteriogram, the lesion should be followed every two to three weeks by repeat studies to check on size and look for new aneurysmal development. Preferably, surgical operation should be postponed until after a complete course of antibiotics because in the inflamed state the aneurysm is friable and the parent artery is necessarily sacrificed. With healing, the aneurysm wall fibroses, allowing placement of a clip.[60] However, if leaking has occurred and if the lesion lies peripherally, arterial ligation preferably should be done early rather than risk complete rupture. Otherwise, the aneurysm should be followed and surgical operation should be done without delay if it is larger on the first follow-up study, or if it is the same size or larger after a complete course of antibiotics.[56]

Psychiatric manifestations occur in up to 50 percent of patients with endocarditis.[47] Hallucinations, confabulation, depression, paranoid ideation, fluctuating confusion and impaired concentration commonly develop, particularly in elderly patients. Endocarditis should always be considered in any unexplained sudden personality change in an older person.

Major retinal complications of endocarditis include hemorrhage, cotton wool patches and a peculiar retinal hemorrhage with a pale center that is erroneously termed a Roth spot.[18,34] Roth, in 1872, described hemorrhages and cotton wool patches in cases of sepsis, terming them septic retinitis; but he did not link them to endocarditis nor did he note the lesion carrying his name.[61] Litten, in 1876, observed the association of endocarditis with retinal hemorrhages containing pale centers and called them Roth spots.[62] This lesion is probably due to a focal accumulation of leukocytes and the cotton wool patches are cytoid bodies.[63] Neither are specific for endocarditis.

Hematologic Manifestations

The leukocyte count is usually normal in patients with S. viridans endocarditis.[35] Leukocytosis in a patient with endocarditis suggests embolic or suppurative complications or a more virulent organism than S. viridans. The circulating polymorphonuclear leukocytes appear to have an acquired intracellular killing defect when compared with those of patients with other forms of acute bacterial infections or of persons used as controls.[64] This defect resolves with the initiation of antibiotic therapy.

Thrombocytopenia with platelet counts as low

as 3,000 to 5,000 per cu mm can occur in SBE,[51,65] and counts under 100,000 per cu mm may be as frequent as 34 percent to 39 percent.[29] The symptom complex of endocarditis with fever, renal insufficiency, neurological manifestations and anemia may suggest a diagnosis of thrombotic thrombocytopenic purpura.[26,66] The bone marrow in instances of thrombocytopenia is normal, showing normal or increased number of megakaryocytes.[29,51,66] Circulating immune complexes are highest at the platelet nadir and decrease when the platelet count returns to normal.[64,66]

Of patients with endocarditis, 75 percent have an anemia.[67] Most commonly, anemia of chronic infection with normocytic normochromic red cells exists but splenomegaly may cause a hemolytic anemia through sequestration,[68] or occasionally a deformed valve may promote intravascular hemolysis.[66]

Coagulopathies are not common associates of Gram-positive infections but the occurrence of disseminated intravascular coagulation (DIC) in S. aureus endocarditis may be more common than suspected.[29,32] In two series of cases of staphylococcal sepsis in which coagulation profiles were attained, the incidence of DIC was 15 percent.[69,70]

Musculoskeletal Manifestations

Musculoskeletal manifestations of endocarditis occur in 17 percent to 50 percent of patients and usually develop early in the course of the disease.[71] Arthralgias and arthritis are the most common complaints and most frequently involve the large joints of the lower extremities.[71] They are fleeting in nature and can affect several joints in an asymmetrical pattern; however, a symmetrical polyarthritis may mimic a collagen vascular disease.[74]

The synovitis is almost uniformly sterile with only rare instances of positive findings on cultures of synovial fluid.[72] Analysis of synovial fluid is not revealing, with 1,200 to 16,500 leukocytes per cu mm with variable predominance of polymorphonuclear cells, negative cultures, negative latex agglutination, normal complement and nonspecific biopsy results showing acute inflammation.[73] The arthritis resolves with antibiotic treatment of the endocarditis.

Other manifestations include myalgias,[71] severe back pain,[71,75] disc space infections,[71] and hypertrophic osteoarthropathy.[33] The cause of the musculoskeletal complaints is probably immune mediated. The common occurrence of monoarticular complaints suggests that a generalized immune complex process does not play a role but rather that an embolus laden with antigen lodges in a periarticular area and initiates a localized immunologic event.[71]

Renal Manifestations

Endocarditis commonly initiates an active urinary sediment with red cells, leukocytes, proteinuria and red-cell casts. Three forms of renal involvement are recognized in endocarditis: (1) infarctions of portions of the kidney from large arterial emboli,[65] which are found in 56 percent of autopsies done in cases of endocarditis;[18] (2) focal glomerulonephritis, which probably is due to either small emboli[12,65] or immune complexes,[11,76] and (3) diffuse glomerulonephritis, which is an immune complex nephritis.[12] Of the three forms, the only one that causes renal insufficiency is the diffuse glomerulonephritis.[12,34]

Renal infarction is usually asymptomatic; but when it is present, flank pain is the major symptom, with hematuria and pyuria.[41] The histology of the immune complex nephritis is the "lumpy bumpy" type of immunofluorescence[12] and is not specific for endocarditis.[65] Deposits of C3 and immunoglobulins are found in the glomerular tufts[10-12] along with bacterial antigen[10] and antibody specific for the invading organism.[77] Electron dense deposits are noted on electronmicroscopy,[12] and peripheral serum complement is depressed.[10-12] Renal histology and function generally improve with antibiotic therapy for the endocarditis.[10]

REFERENCES

1. Bacon PA, Davidson C, Smith B: Antibodies to Candida and autoantibodies in subacute bacterial endocarditis. Q J Med 43:537-550, 1974

2. Lerner P, Weinstein L: Infective endocarditis in the antibiotic era. N Engl J Med 274:199-206, 259-266, 323-331, 388-393, 1966

3. Das SK, Cassidy JT: Importance of heart antibody in infective endocarditis. Arch Intern Med 137:591-593, 1977

4. Sheagren JN, Tuazon CU, Griffen C, et al: Rheumatoid factor in acute bacterial endocarditis. Arthritis Rheum 19:887-890, 1976

5. Williams RC, Kunkel HG: Rheumatoid factor, complement, and conglutinin aberrations in patients with subacute bacterial endocarditis. J Clin Invest 41:666-675, 1962

6. Messner RP, Laxdal T, Quie PD, et al: Rheumatoid factors in subacute bacterial endocarditis—Bacterium, duration of disease or genetic predisposition? Ann Intern Med 8:746-756, 1968

7. Bayer AS, Theofilopoulous AN, Eisenberg R, et al: Circulating immune complexes in infective endocarditis. N Engl J Med 295:1500-1505, 1976

8. Hurwitz D, Quismario FP, Friou GJ: Cryoglobulinemia in patients with infective endocarditis. Clin Exp Immunol 19:131-141, 1975

9. Mohammed I, Ansel BM, Holborrow EJ, et al: Circulating immune complexes in subacute bacterial endocarditis and poststreptococcal glomerulonephritis. J Clin Pathol 30:308-311, 1977

10. Perez GO, Rothfield N, Williams RC: Immune-complex nephritis in bacterial endocarditis. Arch Intern Med 136:334-336, 1976

11. Boulton-Jones JM, Sissons J, Evans D, et al: Renal lesions of subacute infective endocarditis. Br Med J 2:11-14, 1974

12. Gutman RA, Striker GE, Gilliland BC, et al: The immune complex glomerulonephritis of bacterial endocarditis. Medicine (Baltimore) 51:1-26, 1972

13. Robertson JC, Broune ML: Splinter hemorrhages, pitting and other findings in fingernails of healthy adults. Br Med J 4: 279-281, 1974

14. Kilpatrick ZM, Greenberg PA, Sanford JP: Splinter hemorrhages—Their clinical significance. Arch Intern Med 115:730-735, 1965

15. Platts MM, Greaves MS: Splinter hemorrhages. Br Med J 2:143-144, 1958

16. Blum M, Aviram A: Splinter hemorrhages in patients receiving regular hemodialysis. JAMA 239:47, 1978

17. Pelletier L: Infective endocarditis—A review of 125 cases from the University of Washington Hospitals, 1963-1972. Medicine (Baltimore) 56:287-313, 1977

18. Weinstein L, Rubin RH: Infective endocarditis—1973. Prog Cardiovasc Dis 16:239-274, 1973

19. RuDusky BM: Recurrent Osler's nodes in systemic lupus erythematosus. Angiology 20:33-37, 1969

20. Puklin JE, Balis GA, Bentley DW: Culture of an Osler's node—A diagnostic tool. Arch Intern Med 127:296-298, 1971

21. Thadepalli H, Francis CK: Diagnostic clues in metastatic lesions of endocarditis in addicts. West J Med 128:1-5, 1978

22. Osler W: Chronic infectious endocarditis. Am J Med 2: 219-230, 1908-1909

23. Von Gemmingen GR, Winkeimann RJ: Osler's node of subacute bacterial endocarditis—Focal necrotizing vasculitis of the glomus body. Arch Dermatol 95:91-94, 1967

24. Alpert JS, Krous HF, Dalen JE, et al: Pathogenesis of Osler's nodes. Ann Intern Med 85:471-473, 1976

25. Horowitz LD, Silber R: Subacute bacterial endocarditis presenting as purpura. Arch Intern Med 120:483-486, 1967

26. Hall WH: Purpura fulminans with group B beta-hemolytic streptococcal endocarditis. Arch Intern Med 116:594-597, 1965

27. Lawrence EC, Mills J: Bacterial endocarditis mimicking vasculitis with steroid-induced remission. West J Med 124:333-334, 1976

28. Rahal JJ, MacMahon HE, Weinstein L: Thrombocytopenia and symmetrical peripheral gangrene associated with staphylococcal and streptococcal bacteremia. Ann Intern Med 69:35-43, 1968

29. Murray HW, Tuazon CU, Seagren JN: Staphyococcal septicemia and disseminated intravascular coagulation—*Staphylococcal aureus* endocarditis mimicking meningococcemia. Arch Intern Med 137:844-847, 1977

30. Plaut ME: Staphylococcal septicemia and pustular purpura—Report of cases. Arch Dermatol 99:82-85, 1969

31. Davis JA, Weisman MH, Dial DH: Vascular disease of infective endocarditis—Report of immune-mediated events in skin and brain. Arch Intern Med 138:480-483, 1978

32. Watanakunakorn C, Tan JS, Phair JP: Some salient features of *Staphylococcal aureus* endocarditis. Am J Med 54:473-481, 1973

33. McCord MC, Moberly J: Acute hypertrophic osteoarthopathy associated with subacute bacterial endocarditis. Ann Intern Med 39:640-644, 1953

34. Kerr A: Subacute Bacterial Endocarditis. Springfield, IL, Charles C Thomas, 1955

35. Weinstein L, Schlesinger JJ: Pathoanatomic, pathophysiologic and clinical correlations in endocarditis. N Engl J Med 291:832-836, 1122-1127, 1974

36. Vergne R, Selland B, Gobel FL, et al: Rupture of the spleen in infective endocarditis. Arch Intern Med 135:1265-1267, 1975

37. Spencer RP: Healing of a splenic infarct. J Nucl Med 15:303-304, 1974

38. Chulay JD, Lankerani MR: Splenic abscess. Am J Med 61:513-521, 1976

39. Schoenfeld MR, Messeloff CR, Han ST, et al: Large abscess of the heart and spleen complicating bacterial (enterococcal) endocarditis. Am Heart J 61:818-821, 1961

40. Gada LD: Changing clinical pattern of splenic abscess. Am J Surg 128:182-187, 1974

41. Garvey GJ, Neu HC: Infective endocarditis—An evolving disease. Medicine (Baltimore) 57:105-127, 1978

42. Katz D, Cooper JA, Frieden J: Bacterial endocarditis presenting as complete heart block with paradoxical (left-to-right) pulmonary emboli. Am Heart J 85:108-112 1973

43. Banks T, Fletcher A, Ali N: Infective endocarditis in heroin addicts. Am J Med 55:444-451, 1973

44. Ramset RG, Gunnar RM, Tobin JR: Endocarditis in the drug addict. Am J Cardiol 25:608-618, 1970

45. Openshaw H: Neurological complications of endocarditis in persons taking drugs intravenously. West J Med 124:276-281, 1976

46. Jones HR: Neurologic manifestations of bacterial endocarditis. Ann Intern Med 71:21-27, 1969

47. Greenlee JE, Mandell GL: Neurological manifestations of infective endocarditis—A review. Stroke 4:958-963, 1973

48. Ziment I: Nervous system complications in bacterial endocarditis. Am J Med 47:593-607, 1969

49. Cates JE, Christie RV: Subacute bacterial endocarditis. Q J Med 20:93-130, 1951

50. Alexander R, Holloway A, Honsinger RW: Surgical debridement for resistant bacterial endocarditis. JAMA 210:1757-1759, 1969

51. Wilson R, Hamburger M: Fifteen years' experience with staphylococcal septicemia in a large city hospital—Analysis of 55 cases in the Cincinnati General Hospital 1940-1954. Am J Med 22:437-457, 1957

52. Katz RI, Goldberg HI, Selzer ME: Mycotic aneurysm—Case report with novel sequential angiographic findings. Arch Intern Med 134:939-942, 1974

53. Gilroy J, Andaya L, Thomas VJ: Intracranial mycotic aneurysms and subacute bacterial endocaritis in heroin addiction. Neurology (Minneapolis) 23:1193-1198, 1973

54. Ishikawa M, Waga S, Moritake K, et al: Cerebral bacterial aneurysms—Report of three cases. Surg Neurol 2:257-261 1974

55. Hourihane JB: Ruptured mycotic intracranial aneurysms—A report of three cases. Vasc Surg 4:21-29, 1970

56. Bingham W: Treatment of mycotic intracranial aneurysms. J Neurosurg 46:428-437, 1977

57. Moskowitz MA, Rosenbaum AE, Tyler HR: Angiographically monitored resolution of cerebral mycotic aneurysms. Neurology 24:1103-1108, 1974

58. Suwanwela C, Suwanwela N, Charuchinda S, et al: Intracranial mycotic aneurysms of extracranial origin. J Neurosurg 36:552-559, 1972

59. Ziment I: Angiography in the management of intracranial mycotic aneurysms. Arch Intern Med 122:349-362, 1968

60. Cantu RC, LeMay M, Wilkinson HA: The imsportance of repeated angiography in the treatment of mycotic-embolic intracranial aneurysms. J Neurosurg 25:189-193, 1966

61. Roth M: Ueber Netzhaut Affectionen bei Wundfiebern. Deutsch Ztschr Chir 471-484, 1872

62. Litten M: Ueber akute maligne Endocarditis und die dabei vorkommenden Retinal-veranderungen. Charite Ann 3:137-172, 1876

63. Kennedy JE, Wise GN: Clinicopathological correlation of retinal lesions—Subacute bacterial endocarditis. Arch Ophthalmol 74:658-662, 1965

64. Repine JE, Clawson CL, Burchell HB, et al: Reversible neutrophil defect in patients with bacterial endocarditis. J Lab Clin Med 88:780-787, 1976

65. Case 30-1974, Case records of Massachusetts General Hospital: Fever of unknown origin with severe thrombocytopenia. N Engl J Med 291:242-249, 1974

66. Bayer AS, Theofilopolous AN, Eisenberg R, et al: Thrombotic thrombocytopenic purpura-like syndrome associated with infective endocarditis. JAMA 238:408-410, 1977

67. Parsons WB, Cooper T, Scheifley CH: Anemia in bacterial endocarditis. JAMA 153:14-16 1953

68. Joyce RA, Sande MA: Mechanism of anemia in experimental bacterial endocarditis. Scand J Haematol 15:306-311, 1975

69. Corrigan JJ, Jordan CM: Heparin therapy in septicemia with disseminated intravascular coagulation. N Engl J Med 283: 778-782, 1970

70. Colman RW, Robboy SJ, Minna JD: Disseminated intravascular coagulation—An approach. Am J Med 52:679-689, 1972

71. Churchill MA, Gerachi JE, Hunder GG: Musculoskeletal manifestations of bacterial endocarditis. Ann Intern Med 84: 754-759, 1977

72. Tompsett R: Bacterial endocarditis—Changes in the clinical spectrum. Arch Intern Med 119:329-332, 1967

73. Myers AR, Schumacher HR: Arthritis of subacute bacterial endocarditis (abstract). Arthritis Rheum 19:813-814, 1976

74. Bayer AS, Brenner RJ, Galpin JE, et al: Severe disabling polyarthritis associated with bacterial endocarditis. West J Med 123:404-407 1975

75. Holler JW, Pecora JS: Backache in bacterial endocarditis. NY State J Med 70:1903-1905, 1970

76. Messner RD, Williams RC, Keslin MH: Glomerulonephritis with subacute bacterial endocarditis—Immunofluorescent studies. Arch Intern Med 132:578-581, 1973

77. Levy RL, Hong R: The immune nature of subacute bacterial endocarditis nephritis. Am J Med 54:645-652, 1973