OCCULT SUBACUTE BACTERIAL ENDOCARDITIS MANIFESTED BY HEMATOLOGIC ABNORMALITIES, INCLUDING PANCYTOPENIA *

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ANEMIA of variable degree is the commonest hematologic abnormality observed in subacute bacterial endocarditis. The erythrocytes are usually somewhat hypochromic but may be normochromic. Usually the leukocytes are normal in number, but they may be increased, particularly if embolic complications are present. Morphologically, "toxic" changes are apparent in the granulocytes, sometimes accompanied by a shift to the left. The number of platelets has not been consistently altered in cases reported in the literature. The presence of phagocytic reticuloendothelial cells in stained smears of peripheral blood has been demonstrated by many observers in about 15 per cent of cases. Although these cells have been found in other conditions, their presence in the blood suggests bacterial endocarditis. Sturgis [1] stated that phagocytic reticuloendothelial cells may be found in all cases of the disease if a thorough search is conducted by a trained observer.

Occasionally the hematologic picture may be more profoundly disturbed. Rare instances of pancytopenia, one of which is reported here, may be encountered in association with bacterial endocarditis. Such cases may lead to confusion in diagnosis by simulating a primary hematologic disorder. This report presents data on two cases (cases 1 and 2) in which the hematologic abnormalities overshadowed the "classic" manifestations of the disease to such an extent that the correct diagnosis was not established clinically. With modern methods of antibiotic therapy permitting cure in the majority of cases of subacute bacterial endocarditis, it is important to make this diagnosis correctly and as early as possible.

For years clinicians have been familiar with the maxim: "If the patient has a cardiac murmur and an unexplained fever, consider bacterial endocarditis." To this we would add: "If the patient has a cardiac murmur and an unexplained *anemia,* despite the absence of fever, consider bacterial endocarditis." Because of the few cases in which a murmur is an inconstant finding or is considered functional, still another maxim might be formulated: "If the patient has an unexplained fever and *anemia,* despite the absence of a convincing cardiac murmur, consider bacterial endocarditis." If the association of subacute bacterial endocarditis and hematologic abnormalities had been recognized, the following cases (which were difficult diagnostic problems) might have been resolved earlier with the correct diagnosis.

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Case Reports

Case 1. A Negro farmer, aged 44 years, was referred to the Mayo Clinic because of an indeterminate anemia for which he had received six transfusions, the last one having been given one and a half weeks before admission. Iron and liver had been administered without benefit. Predominant symptoms had been weakness and exertional dyspnea. He had lost 22 pounds in the preceding year. There was no history of fever, chills or sweats.

Arthritis involving the spinal column and peripheral joints had been present in varying degrees of severity for 15 years. After an examination 11 years previously, the patient had been told that his heart was enlarged. No other history of antecedent cardiac abnormality could be elicited.

On examination the patient was afebrile and had pallor of his mucous membranes. The heart was enlarged to the left. The cardiac rate was 116 per minute, with regular rhythm. A systolic thrill was felt which was maximal in the second left interspace 3 inches to the left of the midsternal line. A systolic murmur was heard over the entire precordium, loudest over the pulmonic area and along the left sternal border. Blood pressure was 100 mm. Hg systolic and 70 mm. diastolic. Chest expansion was markedly limited, and the spinal column was almost immobile. The spleen was not palpable. A psoriatic eruption was present in the scalp and on both lower extremities.

The hemoglobin concentration of the blood was 10.8 gm. per 100 c.c., the erythrocyte count 3,680,000 cells per cubic millimeter, and the leukocyte count 15,000 cells per cubic millimeter. A blood smear showed the anemia to be normocytic and normochromic; toxic granulation of the granulocytes was also noted. The sedimentation rate of erythrocytes (Westergren) was 56 mm. in one hour. The result of a Beck-Hertz test for sickling was negative. The urine was normal except for albumin, grade 2. A roentgenogram of the chest showed cardiac enlargement. Roentgenograms of the spinal column showed characteristic changes of rheumatoid spondylitis. Roentgen examination of the skull disclosed no abnormality. An electrocardiogram showed left axis deviation and inverted T waves in Leads III, V_1, V_2, and V_5.

Neurologic examination gave negative results when the patient was first seen at the clinic, but just prior to his hospitalization on the following day he noticed that his left arm and leg suddenly became weak. When examined at the hospital, he was found to have left facial weakness and hemiparesis. At the hospital he was seen in consultation by a cardiologist, who stated that the auscultatory findings were not particularly suggestive of a mitral valvular lesion, but the patient was near extremis at the time of the examination.

The patient remained afebrile with the exception of a single reading of 100° F. on the second hospital day. Two days after the onset of hemiparesis, bifrontal headache began and persisted for several days. Following this the patient became weaker and semicomatose. On the twelfth day he suddenly became apprehensive, hyperpneic and cold, and died within a few minutes.

Necropsy revealed subacute bacterial endocarditis of the mitral valve, which was the site of healed rheumatic endocarditis. The heart weighed 480 gm., compared to an average weight of 380 gm. for a man of this size. The myocardium contained multiple embolic abscesses. A large infarct was present in the right parietal lobe of the brain and another in the right kidney. The spleen weighed 525 gm. (normal, 150 gm.).

Comment: Although the findings in this case indicated the presence of organic heart disease, attention was focused on the unexplained anemia which had for months dominated the clinical picture and proved refractory to treatment. In the absence of fever, cellular elements in the urine and a palpable spleen, the relation of the anemia to the cardiac findings was not recognized.

Case 2. A salesman, aged 46 years, was referred to the clinic because of weakness, loss of weight, dyspnea and purpura which had been present for three months. Eight months previously he had first experienced moderate dyspnea while walking through the snow and had had to stop several times within six blocks because of substernal constriction "like a vise." After that he had increasing exertional dyspnea and substernal constriction occurring also during excitement, aggravated by cold weather, and relieved by rest. Beginning three months before admission, he noticed general weakness and a further decrease in effort tolerance. His physician told the patient that he had heart trouble and anemia. The result of a bone marrow examination was said to be normal. The patient was hospitalized for 10 weeks and was given two blood transfusions as well as a number of injections of penicillin. After that he returned to work for four weeks but had to seek medical care again because of progressive weakness, dyspnea and substernal constriction. For the first time he noticed swelling of his legs, which gradually became severe. He also noted red spots on his feet and legs. A cough productive of brown sputum appeared. He estimated that he had lost between 10 and 15 pounds. There was no history of fever, chills or sweats.

On examination the patient was pale and moderately dyspneic after slight exertion. His temperature was 99° F., pulse rate 92 beats per minute, and blood pressure 104 mm. Hg systolic and 54 mm. diastolic. No adenopathy was noted. The heart was moderately enlarged clinically. Occasional premature contractions were detected. One examiner reported a faint systolic murmur at the apex, but subsequent careful examinations failed to confirm the presence of a cardiac murmur. Lung fields were clear. The liver was not palpable. The spleen extended 9 cm. below the left costal margin. Severe pitting edema was present in both lower extremities as high as the knees. Many purpuric spots of various sizes were found from the feet to the buttocks.

The hemoglobin concentration of the blood was 5.5 gm. per 100 c.c., the erythrocyte count 1,730,000 cells per cubic millimeter, and the leukocyte count 2,200, with a differential count of 24 per cent lymphocytes, 7 per cent monocytes, 67 per cent neutrophils, 1 per cent eosinophils, 0.5 per cent basophils and 0.5 per cent late myelocytes. A blood smear showed increased rouleaux formation and erythrocyte regeneration. The platelet count was 44,000 cells per cubic millimeter. Kline and Kahn reactions for syphilis were weakly positive, but further testing gave negative or doubtful results. Urine examinations showed specific gravity of from 1.005 to 1.009, with albuminuria, grade 2, and microhematuria, grades 1 to 2. Bence-Jones protein was not present. Urine cultures and smears revealed no acid-fast bacilli or other pathogenic organisms. The blood urea concentration was 66 mg. per 100 c.c., and the serum protein concentration 6.9 gm. per 100 c.c., with 2.6 gm. of albumin and 4.3 gm. of globulin. The serum contained 0.5 mg. of direct reacting bilirubin and 0.7 mg. of indirect reacting bilirubin per 100 c.c. Roentgen examination of the chest revealed cardiac enlargement, congestion of the pulmonary arteries and small adhesions at the base of the right lung. Roentgenograms of the skull and long bones were normal. An electrocardiogram showed a normal rate and rhythm, low amplitude QRS complexes in Leads I, II and III, and a diphasic T wave in Lead III. The precordial leads were within normal limits. Sternal marrow smears showed hypocellularity, with relatively active erythrocyte regeneration, moderate left shift in the myeloid line and a slight increase in plasma cells.

The findings suggested a primary hematologic disorder. The diagnoses most seriously considered were malignant lymphoma, myelosclerosis with agnogenic myeloid metaplasia, and subleukemic leukemia. On the third day of observation the patient's temperature reached 100° F. and on the fourth day it was 102.8° F. A roentgenogram of the chest at this time showed patchy areas of pneumonitis in the right lower and middle lung field. Penicillin was administered for four days, during which time the temperature returned to normal and remained normal. The patient was given four blood transfusions, a total of 2 liters of blood. After the transfusions his hemoglobin concentration was 5.0 gm. per 100 c.c., the erythrocyte count was 2,050,000 cells per cubic millimeter, and the leukocyte count was 3,100 cells per cubic millimeter. The platelet count was 58,000 cells per cubic millimeter. A tentative diagnosis of malignant lymphoma was reached, and four roentgen treatments were administered to the abdomen as a therapeutic test. The patient was dismissed 17 days after admission and instructed to return within four weeks for further evaluation.

Soon after returning home, however, the patient was hospitalized in another city, where he died 99 days after his initial examination at the clinic. During this period of hospitalization, no cardiac murmurs were heard and no blood cultures were performed. Necropsy revealed subacute bacterial endocarditis involving the mitral valve and, to a slight degree, the aortic valve. Congestive heart failure with congestive hepatomegaly and splenomegaly was present, as was focal glomerulonephritis. The latter complication was believed by the pathologist to be a terminal event.

Comment: This case shows the extreme difficulty encountered when subacute bacterial endocarditis is accompanied not only by anemia but also by leukopenia and thrombocytopenia, simulating a primary hematologic disorder. The pancytopenia was attributed to "toxic" suppression of bone marrow activity, since leukemic infiltration and the hyperplasia usually associated with hypersplenic states were absent. The rather marked splenomegaly was consistent with the tentative diagnosis of an abdominal lymphoma. The brief febrile episode was attributed to pneumonitis. The anginal distress was ascribed to coronary insufficiency resulting from coronary sclerosis complicated by the severe anemia. The thrombocytopenia seemed an adequate explanation for the purpuric lesions. The problem was further complicated by the fact that on only one occasion was a cardiac murmur heard by one observer, and repeated reëxaminations by several physicians failed to confirm this finding.

Although the patient was hospitalized and studied in three institutions, the diagnosis of bacterial endocarditis was not considered by any of the attending physicians, a fact which illustrates the confusion created by the existence of pancytopenia and the absence of many manifestations ordinarily associated with the disease.

While the occasional occurrence of leukopenia or thrombocytopenia has been noted, we are not aware of previous reports of pancytopenia in bacterial endocarditis.

Case 3. A white farmer, aged 60 years, came to the clinic because of weakness and loss of weight for two months and abdominal pain for two weeks. Past history was negative. The patient stated that he had lost 30 pounds in two months and had become progressively weaker. He had been taking iron tablets for one and a half months, without apparent benefit. Two weeks prior to his examination at the clinic he had had two transfusions. For two weeks he had had a crampy, intense pain in his abdomen just under the right costal margin. The pain was worse at night, awakening him from sleep on numerous occasions. Neither coughing nor deep breathing aggravated the pain. There was no history of fever, chills or sweats.

The patient was pale and thin. The results of examination of the heart were negative. Over the anterior and lateral portions of his right lower chest there was impaired resonance to percussion, as well as diminished breath sounds and many râles. His epigastrium and right upper quadrant were tender on deep palpation. The liver was felt at the costal margin. His temperature on admission was normal. On the second day it was 101.4° F. The patient had not been aware of fever prior to admission.

The hemoglobin concentration of the blood was 10.8 gm. per 100 c.c., the erythrocyte count 4,390,000 cells per cubic millimeter, and the leukocyte count 13,400 cells per cubic millimeter, with a differential count of 15.5 per cent lymphocytes, 2.5 per cent monocytes, 79.5 per cent neutrophils, 1 per cent eosinophils and 1.5 per cent basophils. Blood smears obtained on several occasions showed a hypochromic anemia and left-shifted neutrophils which contained toxic granules. The sedimentation rate of erythrocytes by the Westergren method was 63 mm. in one hour. Examination of the urine gave normal results. A roentgenogram of the chest showed an inflammatory lesion at the base of the right lung. An excretory urogram showed no renal shadow on the left; the right kidney was enlarged and mild right ureterectasis was present. Cystoscopy and retrograde pyelography confirmed the presence of a solitary kidney. Culture of the urine gave negative results.

In the first week of hospitalization the patient first had a cough which was productive of thick, tenacious sputum. Bronchoscopy was performed with negative results. On the sixteenth hospital day the temperature, which had been normal with the exception of the reading noted previously, rose to 102° F. At the same time the patient had a rather sudden onset of pleural pain in the left lower portion of the chest and a chill. A roentgenogram of the chest at this time showed pneumonia at the bases of both lungs. Following the institution of chemotherapy, the patient's symptoms subsided and the temperature returned to normal. However, from that time the temperature reached levels of 100° to 101° F. on an average of two days in each week. Blood counts at this time revealed essentially the same findings as those recorded on admission. The patient was permitted to return home 38 days after admission.

He returned to the clinic two weeks later, having become stronger and remained at a constant weight. His temperature had continued to rise on one or two days of each week; the reading on admission was 100.6° F. Examination of the heart and lungs gave negative results. Roentgenograms of the chest were normal. The hemoglobin concentration was 8.5 gm. per 100 c.c., the erythrocyte count 3,960,000 cells per cubic millimeter and the leukocyte count 3,500 cells per cubic millimeter. The sedimentation rate was 43 mm. in one hour. Examinations of stools showed no evidence of occult blood or parasites. Urine examinations on several occasions gave normal results; cultures of the urine were sterile. Roentgen examinations of the entire gastrointestinal tract failed to reveal any abnormality.

The patient continued to have fever as high as 101° F. on one or two days of each week. The heart rate averaged 100 beats per minute. Three months after his first examination at the clinic, the patient was found to have a soft apical systolic murmur. Cultures of the blood were performed for the first time, and *Streptococcus viridans* was readily grown from all of three cultures. Another blood smear was examined and found to contain some monocytes with reticuloendothelial characteristics.

Comment: In this case the association of progressive anemia and fever, even in the absence of a cardiac murmur, might have suggested the diagnosis of subacute bacterial endocarditis. Although it is unusual for cardiac murmurs to be absent throughout most of the course of subacute bacterial endocarditis, this case and the preceding one illustrate that such an occurrence renders diagnosis difficult. A higher index of suspicion, resulting from the unexplained anemia, might have led to earlier performance of the appropriate studies by which the diagnosis was finally reached clinically in the last case.

The variations in the leukocyte count should also be noted. The leukocytosis present on admission was associated with a pulmonary complication which was probably embolic. Subsequent counts revealed a mild leukopenia. When a murmur was heard late in the course of the disease, cultures of the blood were performed and demonstrated streptococci. Reticuloendothelial monocytes were found in stained smears of peripheral blood at this time.

Platelet counts were not performed in this case. However, subsequent review of the blood smears made when the leukopenia was present revealed that the platelets were markedly reduced in number. Although we hesitate to report this as a case of pancytopenia without a more definite quantitative estimation of the number of platelets, the available evidence indicates that a pancytopenia was present at that time. Since the discovery of a murmur soon afterward led to establishment of the diagnosis and institution of antibiotic therapy, no further studies of the platelets were carried out.

General Comment

In 200 cases of bacterial endocarditis which we recently reviewed,[2] 75 per cent of patients were found to have anemia (hemoglobin concentration of less than 12 gm. per 100 c.c. in males, or less than 11 gm. per 100 c.c. in females). Anemia was present more frequently than evidence of embolization (61 per cent), splenomegaly (44 per cent), cardiac enlargement (37 per cent), and clubbing of the fingers (17 per cent). The incidence of anemia was equaled by that of fever (75 per cent), and was exceeded only by the findings of cardiac murmurs and bacteremia, both of which were present in 100 per cent of patients (table 1).

A comparison of the objective finding of anemia with the most frequent subjective symptoms is found in table 2. With the exception of a history of fever, no symptom was present in more than 50 per cent of patients. It will also be noted that the most frequent symptoms were constitutional, nonspecific manifestations. Furthermore, 38 per cent of patients gave no history of rheumatic fever or cardiac abnormality prior to the illness which proved to be bacterial endocarditis.

We were impressed by the fact that the manifestations classically associated with subacute bacterial endocarditis were present in a substantially

TABLE I

Bacterial Endocarditis: Comparison of Frequency of Anemia and "Classic" Manifestations in 200 Cases

Signs	Incidence, per cent
Cardiac murmurs	100
Bacteremia	100*
Anemia	75
Fever (temperature more than 100° F.)	75
Evidence of embolization	61
Splenomegaly	44
Cardiac enlargement	37
Clubbing of fingers	17

* Blood cultures performed in 197 cases.

smaller percentage of cases in our series than in previous reports in the literature based entirely on necropsy material. It is believed that our data, tabulated from clinical evaluation rather than from necropsy findings, represent more accurately the disease as seen by the clinician.

Twenty-eight patients (14 per cent) of our series had received treatment with iron, liver or blood transfusions before admission to the clinic. The diagnosis of bacterial endocarditis had been reached in none of these patients. Failure to establish the cause of the anemia probably delayed diagnosis and institution of proper treatment in the cases just mentioned.

Many patients have been seen in recent years after they have received one or more short courses of antibiotic therapy for a febrile illness which later proved to be bacterial endocarditis. By suppressing the fever and temporarily rendering the blood stream sterile, the antibiotic therapy masks two of the usual findings but does not cure the bacterial endocarditis. In the absence of fever, bacteremia and the less frequent manifestations of the disease, a soft systolic murmur might not be considered significant. Because of the frequent association of anemia and subacute bacterial endocarditis, one may not with assurance explain such murmurs on the basis of anemia alone. In view of these observations, hematologic abnormalities assume great importance in suggesting the diagnosis of bacterial endocarditis.

TABLE II

Bacterial Endocarditis: Comparison of Frequency of Anemia and Frequent Subjective Symptoms in 200 Cases

Manifestations	Incidence, per cent
Anemia	75.0
Fever (history of)	71.5
Loss of weight	41.5
Chills	33.0
Weakness	33.0
Fatigue	27.0
Sweats	22.5
Anorexia	18.0
Headache	15.0
Malaise	11.5
Dyspnea	11.0

Summary

Data have been presented on three cases which illustrate the difficulty in diagnosis which may arise when hematologic abnormalities overshadow the "classic" manifestations of subacute bacterial endocarditis. All three cases showed anemia, which we have found to be present in 75 per cent of cases of the disease. One case had pancytopenia which, to our knowledge, has not been present in any case previously reported in detail. It is emphasized that the association of a cardiac murmur and an unexplained anemia or of an unexplained fever and anemia should suggest the possibility of bacterial endocarditis.

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