Late Cardiac Complications of Chronic, Severe, Refractory Anemia with Hemochromatosis

By Mary Allen Engle, M.D., Marion Erlanson, M.D., and Carl H. Smith, M.D.

Among patients who from infancy have had severe anemia, refractory to therapy and usually requiring transfusions, we have observed the development of one or both of two cardiac complications unusual for anemia alone.\(^1\,\,^2\) One, acute pericarditis, appeared benign but often recurred, whereas the second, congestive heart failure and arrhythmias, led to death within a few months to a few years. These complications coincided with signs of progressive massive overload of iron. We have observed the development of cardiac involvement and acquired hemochromatosis in 41 patients, 39 with thalassemia major and two with regenerative anemia. Nineteen of the 41 patients had pericarditis, 26 had congestive cardiac failure, and 10 patients suffered from both. Six of the 41 developed cardiac enlargement and an abnormal electrocardiogram; four of these died of sepsis before either pericarditis or congestive failure was manifest. Only eight patients who have passed the age of 8 years and have a similar anemia are thus far free from signs of cardiac involvement. There was no predilection of one sex over the other.

Natural History of Acquired Hemochromatosis

An early sign was the appearance in childhood of speckled pigmentation over the entire body but most noticeable on the hands and neck (fig. 1). As the pigment deposition deepened, the skin appeared bronze or slate-gray. Microscopic examination showed deposits of melanin or iron granules, or both. Striking enlargement of the liver and spleen occurred. Splenectomy was performed in most of the patients as transfusion requirements rose due to the development of a hemolytic component of the anemia.\(^3\) By late childhood, growth and weight gain slowed, and the adolescent growth spurt with the development of secondary sexual characteristics.
was retarded or did not occur. The facial appearance of those who reached the late teens or twenties was immature. Only seven of the 41 patients lived to the age of 20 or beyond, and diabetes developed in three of these.

Cardiac Involvement

In these patients with acquired hemochromatosis a systolic murmur, interpreted as hemic, was present from infancy. In late childhood, asymptomatic but progressive cardiac enlargement and electrocardiographic abnormalities appeared. The cardiac complications occurred in this setting, usually in the second decade. The average age at onset of pericarditis, 11 years, was a little earlier than that for heart failure, 16 years.

Pericarditis

Since 1950, 19 patients have had 33 recognized attacks of pericarditis.4 Their ages ranged from 6 to 17 years at the first episode. The acute illness was preceded by fever and heralded by precordial pain, which was made worse by deep inspiration or lying down and was sometimes referred to the shoulder. Pericardial friction rub was present and the electrocardiogram showed the serial changes in ST segments and T waves that are characteristic of pericarditis. Ten patients had gross pericardial effusion during one or more episodes (fig. 2), associated in three instances with pleural effusion. Four patients showed signs of congestive cardiac failure for the first time while they had pericarditis, and one died. In the others, the signs of pericardial involvement cleared spontaneously after a few days to several months, but usually within 2 or 3 weeks. In one patient who died later in chronic, congestive failure many years after her episode of pericarditis, the pericardial sac was obliterated by old, adhesive pericarditis.

Although the course of the illness resembled that of acute, benign pericarditis, its etiology is unknown, since bacteriologic studies revealed no causative organism, and the virologic studies that were done yielded no agent. Of the attacks, 30 occurred between September and May. This would be an unusual seasonal incidence for the one virus that has been identified as a cause of pericarditis, the Coxsackie B virus.5 Infections due to that agent have a peak incidence between July and September. Antibiotic agents did not influence the course of the illness in the first cases; so they were not administered in the more recent ones. Rest in bed and continuance of transfusions were the chief forms of therapy. Ten of the patients with pericarditis also demonstrated the second and more serious cardiac complication: heart failure and arrhythmias.

Figure 2

Congestive Cardiac Failure

The appearance of heart failure in 26 of the 41 patients was insidious in onset. Around the age of 10 years, the heart size on roentgen examination began to increase (figs. 2A and 3A) and a pattern of left ventricular hypertrophy developed in the precordial lead electrocardiogram, while in 15 first-degree heart block appeared. Sinus tachycardia was not present at this stage. Just before the onset of heart failure, an occasional atrial premature contraction was noted in 19 and abnormalities of the T waves appeared in 10 patients.

When signs of congestive heart failure were evident, the patients complained of being more tired than usual, and they noticed shortness of breath on exertion, but most did not come to the hospital until swelling of feet and legs was evident. New cardiac findings at this time included tachycardia and a gallop rhythm, in addition to marked cardiomegaly, venous distention, and pitting, dependent edema. The liver was already so huge and firm from extramedullary hematopoiesis and hemochromatosis that one could not judge any increase in its size that could be attributed to the heart failure. As is true for most children in failure, the younger patients did not have rales in the lungs, although most were orthopneic and several had a cough. Rales were heard in the adults, however. Cardiac output had not been measured in these patients when the anemia was their only problem, and it was not measured as cardiac involvement developed. It can only be assumed that the cardiac output was lower when frank congestive failure occurred.

The size and shape of the enlarged heart and the diminished pulsations on fluoroscopy often raised the question whether cardiac dilatation or pericardial effusion or both were present. This problem was resolved by angiocardiography in a few patients (figs. 2B and 3B). That study showed whether the enlargement was due solely to dilatation of cardiac chambers (fig. 3) or whether a halo of unopacified pericardial fluid surrounded the heart (fig. 2). In none of the patients who came to postmortem examination was there gross pericardial effusion.

The ages of the 26 patients when cardiac failure occurred are shown in table 1. The peak incidence was between 10 and 15 years, and it had developed in most before the age of 20. The two oldest patients, aged 27 and 31 years, were considered to have an intermediate form of thalassemia, less severe than the others, and had not received transfusions until adulthood. The table summarizes the data on the patients with heart failure according to age at onset, as well as therapy for the anemia, the electrocardiographic changes, and postmortem findings.
Arrhythmias and Heart Block

Along with the heart failure, more serious disturbances of rhythm and conduction appeared than had previously been present (fig. 4). Nineteen had atrial arrhythmias. Sustained arrhythmias as well as frequent premature beats and short runs of supraventricular tachycardia and atrial flutter and fibrillation were seen. Twelve patients had ventricular premature beats, and three had repetitive ventricular tachycardia.

Atrioventricular block worsened. The PR interval was as high as 0.32 second in one patient with first-degree heart block. Three had second-degree heart block with dropped beats. Complete heart block developed in two patients. Intraventricular block appeared in nine patients (eight right and one left bundle-branch block). Six lost the voltage criteria for left ventricular hypertrophy.

Treatment

Digitalization, salt restriction, diuretics, rest in bed, oxygen, and continuance of transfusions of packed red cells were employed. Patients who improved were maintained on digitalis, salt restriction, and diuretics. Electrolyte balance was regulated by appropriate oral intake. The supraventricular arrhythmias responded to digitalization, and the episodes of ventricular tachycardia were controlled with procaine amide, initially administered intravenously and then followed by oral maintenance therapy. Use of chelating agents to remove some of the excess iron is under investigation.

Deaths

Although most patients showed some improvement initially, 25 of the 26 died in heart failure. The duration of life after the onset of failure was less than 3 months in over half of the patients, and nine died within 1 month of the appearance of failure (table 1). Four other patients with signs of hemochromatosis and cardiac involvement died of sudden, overwhelming sepsis before heart failure occurred.

Postmortem Findings

Autopsy was performed on 11 patients who...
Congestive Heart Failure in 26 Patients with Chronic, Severe Anemia

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age at onset (years)</th>
<th>Duration to death (months)</th>
<th>Gm. of Fe Transfused*</th>
<th>Years of transfusion Rx</th>
<th>Splenectomy (age in yrs.)</th>
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* Calculation based on 250 mg. of Fe in 500 ml. whole blood or 300 ml. packed cells.

died in heart failure and on three with clinical signs of cardiac involvement who died of sepsis before congestive failure occurred. Except for some variations in severity, the findings in all were remarkably similar. There was widespread iron deposition and fibrosis in the tissues, characteristic of hemochromatosis, and especially marked in the liver, pancreas, gonads, thyroid, pituitary, and adrenal glands, as well as in the kidneys, mucosa of the gastrointestinal tract, and the lymph nodes. The spleen was found to be similarly affected. In those patients on whom permission for necropsy was denied, the spleen and the biopsy of the liver at the time of splenectomy showed these same changes.

About 30 ml. of fluid were present in the pericardial sac of all but one patient, whose sac was obliterated due to adhesive pericarditis (case I.C., table 1). The heart was dilated as well as hypertrophied, in some to more than twice the expected weight.
was stained a deep, rust-brown color. On microscopic examination (fig. 5) large amounts of iron were found in muscle cells and in histiocytes. Focal degeneration and fibrosis were extensive. Myocardial fibers varied in size and in iron content. In some, as much as two thirds of the cell appeared filled with iron. Other myocardial fibers stained poorly, and the nuclei were abnormal or were absent. In many fibers sarcoplasm was devoid of striations and the cells were vacuolated. Masson stain demonstrated marked fibrosis. Prussian blue stain brought out the iron deposition.

**Discussion**

The widespread infiltration, destruction, and fibrosis in the myocardium seemed an adequate explanation for the progressive cardiac enlargement and heart failure, and for the block in atrioventricular and intraventricular conduction as well as for the atrial and ventricular arrhythmias that were observed. The explanation for the unusual susceptibility to episodes of pericarditis was not apparent.

The age and sex distribution of these patients with acquired hemochromatosis and
congenital anemia is different from that described in idiopathic hemochromatosis, in which the peak incidence is between 45 and 55 years with the male sex predominantly affected, and for transfusional hemochromatosis, in which most patients have been over the age of 30 years. Common to all three groups, however, is the excessive absorption and deposition of iron with destruction and fibrosis in the tissues. In all three, congestive cardiac failure is the leading cause of death. Pericarditis, however, has not been a prominent feature in idiopathic or transfusional hemochromatosis. Its prevalence in our patients may represent an increased susceptibility to infection in this group, 16 of whom have undergone splenectomy. It is possible that iron deposition in the myocardium may render the epicardial layer and pericardial sac liable to inflammation in the presence of a virus or other agent capable of causing pericarditis.

The precise mechanism of the abnormal absorption and storage of iron as well as the alteration of tissue structure and function is not clear. Although most of our patients received transfusions every few weeks for life to maintain a hemoglobin level above 7 to 8 Gm. per cent, and thereby were given between 28 and 104 Gm. of iron by the time heart failure occurred, there were two who received only a few transfusions, containing 2.6 Gm. and 4.5 Gm. of iron, and one who had no transfusions at all (Table 1). Prior to 1950 these patients also received oral iron medication in liberal amounts. Regardless of the manner in which they received iron, the end result was the same: the development of hemosiderosis and hemochromatosis, with cardiac complications the chief cause of death. Once the signs of cardiac involvement were manifested, treatment was only temporarily of benefit, just as in other severe, diffuse myocardipathies. The events described were not those of heart disease due to anemia per se, but, rather, those of hemochromatosis. They were the sequel to refractory anemia of the particular form in which there are hypochromia and excessive absorption of iron and in which the only treatment that enabled the patient to survive resulted in the complication that ultimately caused his death.

Summary

Four fifths of 49 patients with chronic, severe anemia from birth have manifested, usually during the second decade, signs of hemochromatosis with cardiac involvement. Nineteen patients had 33 attacks of pericarditis. Congestive cardiac failure with arrhythmias developed in 26 patients, and all but one died with this complication. Four others died of sepsis before heart failure was evidenced. Postmortem examination showed hemochromatosis with severe myocardial involvement.

Acknowledgment

Miss Ethel Longo took the many serial electrocardiograms on these patients. Drs. Gertrude Stern, Irving Schulman, Renee Brilliant, Henry P. Goldberg, Tomiko Ito, Kathryn Ehlers, and the pediatric house staff contributed greatly to the management of the patients. Photomicrographs of the heart were kindly provided by Drs. John Ellis and Jack Hagstrom. Dr. Israel Steinberg performed the angiocardograms.

References

COMPLICATIONS OF CHRONIC ANEMIA


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William Harvey: Unsolved Problems

Although there was no doubt in Harvey's mind concerning the circular movement of the blood, much remained to be clarified. He was still uncertain of many matters.

Each heart beat occurred within such a short space of time that it was impossible to observe its details. Yet he could only explain his ever-recurring questions if he could observe the series of details which made up the movements.

He saw that one movement was not a simple contraction or dilation, but rather a rapid snakelike writhing running through the heart, followed by the next one, just as rapid, so that he was never able to observe the whole and so very significant series of consecutive details one by one.

As he watched the animal during an experiment, he found that it inhaled the air increasingly slowly and that the heart, which to begin with beat so rapidly, became sluggish, then beat only intermittently. Anyone else would have left his victim at that point and gone to seek to prove his preconceptions on a fresh animal. But he waited, watched the paralyzed heart, which gave another twitch and then stopped once more. And then again another sluggish contraction took place.

Thus Harvey was given what he wanted. A slow-motion picture of the process of the heart function. The movement which in its lightning rapidity was incomprehensible was now quite perceptible at this slow pace, not only to the eye but to the touch. He could feel the heart lose intensity; it grew soft and loose, but when it beat, it was taut and hard. And the warmth of the finger could induce a few more contractions in a heart thought to be dead, until finally it lay still and limp, with all power of movement gone. —Tibor Doby, M.D. Discoverers of Blood Circulation. From Aristotle to the Times of Da Vinci and Harvey. New York, Abelard-Schuman, 1963, p. 197.

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