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The Heart in Anemia

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That reduction in the oxygen carrying capacity of the blood has important effects on the normal as well as the diseased heart is not fully appreciated by many. This discussion will be concerned not only with the effect of anemia on the normal and the diseased heart but also with its effects on respiration and the metabolism of the tissues.

Many comprehensive discussions of the pathologic physiology of the cardiovascular and respiratory systems in anemia have appeared in current medical literature during the past years.1, 5, 8 These are excellent sources of basic information for those interested in the complex problems of the physiologic adjustment to diminished oxygen-carrying capacity of the blood. In the present discussion, a less formal pattern will be adopted. At times statements will be made in the spirit of expressed personal opinion, obviously not based upon documented data. This is premeditated, for, convinced that many aspects of the total problem need additional study, we wish to be provocative.

Much of the obvious inconsistency in the great mass of published data stems from the failure of observers to be sufficiently critical of the type of patient selected for study. It is our conviction that any patient who has a varying degree of anemia, regardless of its duration, is not chronic from the standpoint of physiologic adjustment; acute stresses from a varying intensity of anemia introduce emergency reactions which do not operate in the fully acclimatized true “chronic anemia” seen in its most classic form in some parasitic anemias.

Four principle mechanisms may operate in anemia to maintain a normal or near normal oxygen supply to the tissues. These processes never function singly; the importance of each in a particular case depends upon the severity and the duration of the anemia. The four mechanisms are indicated by the following facts:

1. The cardiac minute volume output is increased.
2. The velocity of blood flow is increased.
3. The removal of a greater percentage of oxygen from each gram of circulating hemoglobin results in increased oxygen delivery to the tissues without burdening the heart.
4. Selective shunting of blood to vital organs from areas of lesser importance is a process which operates in normal individuals but is developed more selectively and in greater magnitude during the stress of chronic anemia.

An increase in cardiac output in patients with anemia has been consistently demonstrated by most investigators, but the magnitude of the increase is not well correlated with either the degree or duration of anemia. The cardiac output is usually increased when the hemoglobin is 7 Gm per 100 cc. or less;5, 6; nevertheless, there are many exceptions. The predictable cardiac output in anemic patients is more consistently related to pulse rate and velocity flow than to the hemoglobin level.8 This, however, is true only in anemias of varying degree or of short duration. When one investigates patients with parasitic anemia with relatively constant hemoglobin levels over periods of years, an increased cardiac output at rest is not indicated either by tachy-
cardia or by increased rate of velocity flow. Data obtained under basal conditions in five patients of 23 to 49 years of age with hookworm anemia illustrate the point in question (table 1). The subjects in table 1 were selected for study because of their ability to work as laborers without distress.

A review of the data in table 1 indicates that these individuals under resting conditions very likely did not have an increase in cardiac output, but were able to meet basal oxygen requirements by other mechanisms. The pulse rate averaged 70 per minute. The diastolic blood pressure was low, averaging 56 mm. The circulation time, sodium cyanide method, basilic vein–carotid sinus, averaged 19 seconds.

**Table 1.** Physiologic Data in Hookworm Anemia

<table>
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<tr>
<th>Age, Yrs.</th>
<th>Ht. Rate/Min.</th>
<th>B.P. (mm. Hg)</th>
<th>Cir. Time (sec.)</th>
<th>Hgb. (Gm./100 cc.)</th>
<th>Venous Press. (mm. H2O)</th>
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* Arm to carotid sinus circulation time, sodium cyanide method.

† Crude pulmonary circulation time.

If the volume of cardiac output per minute is determined by rate of cardiac filling and pulse rate, it is improbable that these patients had an increased cardiac output under resting conditions. However, when they were subjected to physical stress in the form of standardized exercise, the cardiac rate increased from 70 to 97 per minute. The diastolic pressure was unchanged, while the average systolic pressure increased from 110 mm. to 132 mm. Hg and the average circulation time decreased from 19 seconds to 11.8 seconds. Even though no cardiac output studies were done, we conclude that under basal conditions of rest no cardiac stress was caused by the anemia in these compensated individuals, but when they were subjected to physical stress, increased cardiac output operated jointly with other mechanisms to supply the increased demand for oxygen.

The increased cardiac output results from an increased pulse rate, acceleration of cardiac filling, and increased stroke volume with no increase in peripheral resistance.

We suggest that tachycardia and increased velocity flow are not physiologically adapted to prolonged strain but rather are mechanisms to meet acute bodily stresses such as fever, exercise, hypermetabolism, and acute anemia.

A review of our accumulated clinical material impresses us with the significant difference in the state of the heart in the ambulatory, physically active, anemic patient, and the patient who is inactive and as a rule confined to bed with essentially the same degree of anemia. We have studied many ambulatory patients with severe anemia and gross cardiac enlargement who show rapid reduction in cardiac size following bed rest without significant change in the degree of anemia. We have not seen unequivocal myocardial hypertrophy, post mortem or by reliable clinical technics, in an anemic patient unless he had been physically active during most of the period of the anemic state, or unless some intrinsic cardiac disease or hypertension coexisted.

The most frequent symptom is dyspnea on effort. The vital capacity of the lungs is a simple, sensitive index of the pulmonary reserve available for augmented respiratory function. The greater the vital capacity, the greater the margin of reserve between comfortable and uncomfortable breathing when increased pulmonary function is necessitated by an augmented volume of pulmonary blood flow. We have found pulmonary ventilation consistently increased on exercise in anemic patients with hemoglobin of 7 Gm. per 100 cc. or less. This occurs in normal individuals, but the difference between the anemic and normal person is in the greater magnitude of increase in anemic individuals with an equivalent amount of work. This encroachment on respiratory reserve predisposes to dyspnea.

It is not surprising that a lowered vital lung capacity has been observed in many anemic subjects. With the passage of time in the completely acclimatized individual, ventilating capacity may be definitely increased beyond normal, approaching that of the athlete.
Patients of this type are capable of much physical work even in a tropical climate in the presence of high degrees of anemia. To discuss the many biochemical and biophysical factors which operate in the dyspnea of the anemic patient is beyond the scope of this paper. A review of published data emphasizes the need for much additional work with special emphasis on the physiologic state of the adequately acclimatized anemic patient who, by virtue of the perfection of compensatory mechanism, can accomplish much physical work.

Individuals with parasitic and other chronic anemias may exhibit more intense pallor than the hemoglobin levels indicate. This is similar to the pallor of myxedema which is due not only to the changes in the quality of the skin but to a reduced peripheral circulation. Plethysmographic measurements of the extremities show diminished blood flow in the hands. Direct observations on the capillaries of the finger-nail fold in anemic patients show marked vasoconstriction; the flow is slow. Our unpublished data are similar. The observations of Bradley and Bradley indicate greatly diminished renal blood flow in chronic anemia consequent to localized vasoconstriction of the afferent arterioles supplying the nephron. The renal blood flow in anemia may be reduced to a third or a half; yet the amount of plasma presented for filtration per unit of time is almost normal because of the low hematocrit values. Nitrogen retention is consequently uncommon unless primary renal disease coexists; however, some impairment of tubular function is usual, probably as a result of anoxia.

These observations indicate that the state of the vascular bed is not constant but varies according to the need for oxygen in different areas of the body. The selective shunting of blood from areas of lesser physiologic importance to more vital ones is effective in maintaining physical fitness. Since there is normally abstraction of 90 per cent or more of the oxygen from the coronary blood during its passage through the myocardium, serious degrees of myocardial anoxia can be prevented in anemia only by great increases in the volume of coronary blood flow by the shunting of blood to this vital organ. That this does happen, there is little doubt, but direct observations on the volume of coronary blood flow in anemic patients both at rest and during stress of physical work are needed.

Numerous electrocardiographic studies in acute and chronic anemia indicate minor changes in approximately 20 per cent of the subjects. The changes are not specific for anemia and are usually minor in degree. Our observations and those of Hunter reveal that in the few patients showing gross abnormalities, no improvement in the electrocardiogram occurred in spite of successful treatment of the anemia. A review of our cases of chronic parasitic anemia shows the interesting fact that of those patients with irreducible cardiac enlargement, 86 per cent showed electrocardiographic changes indicating left ventricular preponderance. This is not conclusive evidence of increase in muscle mass, but it is highly suggestive when correlated with irreducible enlargement.

The heart is the one organ which shows significant physical changes in chronic anemia. Bamberger in 1857 concluded that cardiac enlargement was a frequent result of chronic anemia. Irvine in 1877 and Barrs in 1891 attributed the bruits in chlorotic anemia to cardiac dilatation. Gautier in 1899 recorded his observations in 22 cases of chlorotic anemia and found cardiac enlargement by percussion in 20. Cabot and Richards in 1919 observed cardiac hypertrophy in a patient dying of pernicious anemia in whom no other factor existed to account for the enlargement. In 1927, we studied a patient with hookworm anemia with hemoglobin of 2.9 Gm. per 100 cc. and a cardiothoracic ratio of 62 per cent. The heart size returned to a cardiothoracic ratio of 49 per cent when the hemoglobin increased to 14.6 Gm. per 100 cc. Ball in 1931 was the first to report a case of severe anemia studied with the aid of a teleoentgenogram recording a reduction in heart size with the relief of anemia. Ellis and Faulkner in 1939 studied 47 patients with varying types and degrees of anemia. Of the 38 cases studied by x-ray, 20 showed cardiac enlargement. Later observations in 26 of these patients showed decrease in heart size in 18, with im-
provement in the hemoglobin level. In 1937 one of us reported the results of detailed studies on 18 cases of chronic parasitic anemia. It is significant to note that all of these patients were ambulatory and many were doing physical work. This study showed increased cardiac size in all these patients. The data indicated that the increase in heart size in a few patients was due to reversible dilatation; in others it was due to reducible dilatation and hypertrophy, and in a third group, to definite hypertrophy unassociated with reducible dilatation.

The potential ill effect of anemia on the diseased heart or on the heart laboring under the stress of hypertension, hyperthyroidism, valvular heart disease, pregnancy, arteriovenous fistula, or on the senile heart is a clinical problem of major importance. In many of these conditions high output failure is the rule. It is recognized that in these patients, relief of the failure is rarely satisfactorily accomplished until the condition responsible for the increased cardiac output is eliminated. The relief of anemia may be a deciding factor between recovery or intractable failure.

Many observers have reported the occurrence of angina of effort in patients with anemia. Complete relief of angina pectoris by appropriate treatment of the anemia has been observed. Such patients are admittedly rare and are invariably in the age group in which coronary arteriosclerosis is common. There have been several case reports of angina and anemia in which no evidence of coronary artery disease was found at post-mortem examination. It is our conviction that in such patients the lumen of a small twig of a coronary artery was lessened by arteriosclerosis, which is difficult to demonstrate post mortem. As previously mentioned, the normally large utilization of arterial oxygen by the heart predisposes to ischemic muscle pain in the area supplied by an artery with a narrowed lumen and inelastic wall. The three patients reported by one of us in 1932 and four additional patients observed since then support our belief that angina of effort occurs in patients with anemia only when the coronary arteries are abnormal. Six of the seven patients were carefully followed. Four have died from coronary artery occlusion, one has had myocardial infarction, and one is of particular interest. This patient had pernicious anemia; he was temporarily symptom-free when the hemoglobin was 8 or more Gm., but for the past 14 months he has been unable to walk even slowly on a slight incline unless the hemoglobin is 15 or 16 Gm. per 100 cc.; this suggests progressing coronary artery disease. Our conclusion is that in the few patients who have the anginal syndrome associated with anemia and are rendered free of symptoms by relief of anemia, the complete diagnosis should be angina pectoris resulting from coronary insufficiency.

It is generally appreciated that a systolic murmur is frequently heard at the mitral area in anemic patients. Such murmurs occasionally are heard over the base of the heart at the aortic area, but more frequently over the second and third left intercostal areas. These murmurs are rarely accompanied by significant thrill, are best heard in the recumbent position, are increased in intensity by exercise or amyl nitrite inhalation, and are frequently associated with a snapping quality of the first cardiac sound quite suggestive of mitral stenosis. These elusive apical phenomena are found in their most significant form following the hemolytic crises of sickle cell anemia. Joint pains and fever frequently accompany the crises, resulting in a clinical syndrome quite similar to rheumatic fever and rheumatic heart disease. It is our impression that these signs are more closely related to the accelerated circulation and tachycardia than to the degree of anemia. The mitral signs are best heard when the bell of the stethoscope straddles the intercostal space and is lightly applied to the chest wall. As a rule the snapping quality of the first sound will disappear if the bell of the stethoscope is pressed firmly to the chest wall and against the lower margin of the rib rather than over the intercostal muscles; this is not observed in mitral stenosis.

Aortic diastolic murmurs accompanied by the peripheral phenomena of aortic regurgita-
tion are uncommon. Of the 34 anemic patients studied by Hunter, only one had an early diastolic aortic murmur. We have observed a diastolic aortic murmur with the vascular phenomena of aortic regurgitation only twice since our interest in the heart in anemia became intense about 1925. In both of these patients, the anemia was severe with hemoglobin values of 2.6 and 3.1 Gm. per 100 cc. In each case there was gross cardiac dilatation; the aortic phenomena disappeared with bed rest and reduction in cardiac size before there was significant change in the degree of anemia. The diastolic murmur and fever which frequently accompany severe anemia may suggest bacterial endocarditis or active rheumatic heart disease. Prompt change in the cardiac phenomena following bed rest and appropriate treatment of the anemia simplifies the differential diagnosis.

We agree with Hunter that with the exception of aortic diastolic murmurs, there is no constant relationship between the degree of cardiac enlargement and systolic murmurs. It is our impression that the murmurs are more related to cardiac rate and velocity of blood flow than to either cardiac size or reduced oxygen carrying capacity of the blood.

In many anemic patients the physical signs and symptoms, including edema, strongly indicate heart failure of the congestive type. A detailed study of many such individuals has convinced us that congestive failure does not result from anemia in patients whose hearts are otherwise normal. If true congestive failure occurs with elevated venous pressure, hepatomegaly, orthopnea, and paroxysmal dyspnea, the coexistence of intrinsic cardiovascular disease is almost certain. The prognosis of congestive heart failure in the anemic patient is good, however, if the anemia can be successfully corrected.

**Summary**

The following brief summary seems justified from the large volume of accumulated data dealing with the reaction of the cardiovascular system in the anemic patient.

There are four mechanisms operating in the anemic patient which may increase the supply of oxygen to the tissues when the oxygen carrying capacity of the blood is reduced. Under conditions of rest, a rapid velocity flow and tachycardia with an increase in minute volume of cardiac output is the first response to anemia. As compensation develops, tachycardia and increased velocity flow are largely replaced by selective shunting of blood and the removal of an increasing percentage of oxygen in the tissue capillaries from each gram of circulating hemoglobin.

These later physiologic mechanisms are best illustrated by patients with chronic parasitic anemias. Under conditions of physical stress each of the four physiologic mechanisms contribute in meeting the demands for increased oxygen requirements. Compensation is, however, never perfect; the status of the patient is determined by the reduction in hemoglobin, the tissue oxygen requirements, the presence of physical changes in the cardiovascular and pulmonary systems, degree of oxygen abstraction from the blood, and the selective shunting of blood.

In relatively acute anemia, dyspnea readily occurs on physical exercise. Reduction in the ventilatory capacity of the lung occurring in some anemic patients results from an over-all reduction in physical fitness due to the anemic state rather than to physical changes in the lung. In well compensated, chronic anemia, the vital capacity of the lungs is frequently above normal and similar to that observed in athletes and completely acclimatized, high altitude inhabitants.

In the absence of cardiovascular disease or physical or metabolic factors requiring increased cardiac output, true congestive heart failure rarely results from the anemic state.

Effort angina is uncommon in anemic patients and when present is usually related to underlying coronary artery disease.

Cardiac hypertrophy under certain conditions results from prolonged anemia. Since cardiac hypertrophy is rightly placed in the category of organic heart disease, one is justified in classifying chronic anemia as one of the
etiolologic factors in the production of heart disease.

REFERENCES


