THE CARDIOVASCULAR SYSTEM IN ANEMIA

WITH A NOTE ON THE PARTICULAR ABNORMALITIES IN SICKLE CELL ANEMIA

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That the cardiovascular system is influenced by anemia is generally recognized. Almost sixty years ago Strümpell noted palpitation as one of the first symptoms of severe anemia. He observed that breathing is hurried, owing to a feeling of air hunger and shortness of breath, and that a feeling of oppression in the breast is characteristic. Bamberger nearly a century ago pointed out that cardiac enlargement is found in many patients suffering from anemia. The extent to which the functional activity of the cardiovascular apparatus is affected by anemia, however, is not so generally appreciated. Changes in the heart and circulation develop in part in response to needs arising from the lack of hemoglobin and thus of oxygen per unit of blood, and in part as a result of the influence of the anemia on the heart itself.

Rapid development of anemia is accompanied by shortness of breath, tachycardia, and pallor. Very severe anemia, if produced quickly, as after severe blood loss, results in shock. Here we deal with a failure of adjustments to the lack of oxygen-transporting material as well as with the effects produced by a sharp reduction in total blood volume. In cases in which serious cardiac damage is already present, coronary thrombosis or cardiac failure has been known to develop after severe hemorrhage. In chronic anemia, on the other hand, a severe grade of anemia seems to be well tolerated in many instances. This is no doubt due to the maintenance of an essentially constant blood volume as well as to the opportunity for physiologic adjustments. It is to cardiovascular manifestations associated with chronic anemias that chief reference will be made here.

In chronic anemia the symptoms may be merely moderate dyspnea and palpitation, or there may be tachycardia and precordial pain. Physical findings may include edema of the ankles, apical systolic murmur, lateral displacement of the left cardiac border, downward extension of the liver border, basal systolic murmur, basal râles, and liver tenderness. In a series of 300 cases of pernicious anemia, Carter and Traut found these symptoms and signs appearing in frequency in the order named.

Several writers have reported cases in which the initial and presenting complaints in a case of chronic anemia were those of congestive cardiac failure, and every internist of some experience can recall such cases. In the Indian Medical Service, Gunewardene called attention to the frequency of heart failure in ancylostomiasis. In these cases treatment and cure of the infection and the associated anemia were

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accompanied by disappearance of symptoms of failure, reduction in size of the heart, and disappearance of the murmurs.

Herrick (1918) was one of the first to call attention to the association of pernicious anemia and angina pectoris. Cary Coombs in 1916 found this combination in 9 of a series of 36 cases of pernicious anemia. In Cabot's cases it was demonstrated that the symptoms of angina occurred in persons showing no changes in the coronary arteries. Pickering and Wayne described cases of intermittent claudication as well as angina pectoris in association with anemia, and Zimmermann has also reported angina pectoris in association with severe anemia. There is no doubt that in many of the reported cases, the background for the development of cardiac dysfunction existed before severe anemia developed. Nevertheless, the symptomatic improvement that followed relief of the anemia, speaks for the significance of the anemia in precipitating the cardiac symptoms. Thus in 6 of Pickering and Wayne's cases, the anginal pain did not continue after the anemia was cured, and the tolerance to exercise improved as the hemoglobin level rose. Claudication disappeared permanently in 6 of 7 cases after relief of the anemia. Significant also in regard to the role of anemia as a cause of angina is the fact that, among cases of angina associated with anemia, females have presented this symptom as often as or more often than males; this is in marked contrast to the sex incidence of angina associated with organic heart disease. Furthermore, the mortality of anemic patients with angina is low—approximately from 3 to 10 per cent as compared with about 40 per cent for cases of anginal pain associated with organic heart disease.

Cardiac enlargement in anemia, without other etiologic basis, has been observed repeatedly. The largest heart weighed 710 Gm. Porter observed a heart weighing 610 Gm. in a man who died of hookworm anemia. The heart is often symmetrically enlarged. German and Austrian clinicians of the nineteenth century studied this subject and noted that the heart became smaller when the anemia was relieved. The return to normal size may occur within a very few weeks. Cardiac enlargement has been observed more frequently in patients with particularly low hemoglobin levels and also in children, as well as in the oldest age groups. This has also been demonstrated in association with anemia produced by hemolysis and in anemia produced experimentally, as well as in miscellaneous forms of anemia. The greater the degree of the anemia, the more likely is the heart to decrease in size after improvement. Dilatation as well as hypertrophy must be a factor in the cardiac enlargement. It seems likely that anemia of short duration results in cardiac dilatation that can be completely overcome with relief of the anemia, whereas in cases of long duration hypertrophy takes place.

That systolic murmurs frequently develop in patients suffering from anemia is well known. In one series of cases, apical systolic murmurs were the most frequent; in another, the murmurs were equally divided between the apex of the heart and the area about the second or third interspace to the left of the sternum. Next in frequency are aortic systolic murmurs; these are high-pitched and blowing in character. In children the apical systolic murmur may be transmitted to the axilla and even to the back. Diastolic murmurs, though much less frequent, may occur in the absence of organic heart disease. The usual diastolic murmur is early and blowing
in character and is best made out in the third left interspace near the sternal border. It may be basal or apical in location. Diastolic murmurs have been described only in association with very severe grades of anemia.\textsuperscript{18}

In many cases of severe anemia, electrocardiographic changes have been noted.\textsuperscript{1, 12} The most common change is depression of the R-T (S-T) junction, with a u shaped deformation of the S-T segment and flat or inverted T waves, but without corresponding changes in the QRS complex. The changes are in no way specific and resemble those known to occur in severe cardiac anoxia (coronary insufficiency) or those seen when toxic myocardial effects are present. They often resemble the changes produced by digitalis (changes in the ventricular gradient of the heart muscle). Changes in the deviation of the electrical systole (Q-T interval) and disturbances in AV conduction have been noted occasionally. Such alterations in electrical conduction have been observed chiefly when the anemia was very severe, with a hemoglobin level of 4 or 5 Gm. or less. Reversal of these changes when the blood was restored to normal has occurred.

In any given case of anemia the manifestations related to the cardiovascular system will naturally depend on many factors, namely: (i) the degree of anemia; (ii) the rapidity of development of anemia; (iii) the age of the patient and the capacity of the cardiovascular system for adjustment; (iv) the previous state of the cardiovascular system.

THE PHYSIOLOGIC ADJUSTMENTS TO ANEMIA

In the accompanying diagram (fig. 1) an attempt is made to indicate the physiologic adjustments to anemia that take place in the cardiovascular system. This is purely schematic, for the exact details and quantitative relationships have yet to be worked out. Important contributions on this subject have been made by Blumgart and his associates,\textsuperscript{15} by Stewart and his co-workers,\textsuperscript{16} and by a few other investigators.\textsuperscript{17, 18} The most recent study of note is that of Sharpey-Schafer.\textsuperscript{20} The clinical evidences of an adjusting circulation in cases of anemia are to be found in the rapid heart rate, increased arterial pulsation, increased pulse pressure, and even capillary pulsation in the finger tips. Sharpey-Schafer,\textsuperscript{20} noting this “hyperkinetic syndrome,” as Harrison calls it, described “pistol shot” sounds over the arteries in his cases, positive Duroziez sign, and systolic murmurs on auscultation of the eyeball.

An increase of cardiac rate and in the velocity of blood flow results in greater minute-volume output. The circulation time is reduced. It has been shown repeatedly that the cardiac output is increased in anemia. This may be preceded by a rise in pressure in the right auricle.\textsuperscript{20} At what level of anemia a significant increase occurs is not so certain. Some investigators set this level at 50 per cent hemoglobin. The increase in cardiac output when the hemoglobin has fallen to 30 per cent has been said to be as much as 200 per cent. Employing the cardiac catheterization technic and the direct Fick method, Sharpey-Schaier\textsuperscript{20} observed cardiac outputs varying from 7.4 to 13.4 liters per minute in cases of posthemorrhagic anemia with hemoglobin levels that varied from 25 to 68 per cent, as compared with a normal average cardiac output of 5.3 liters per minute.
The falling viscosity of the blood, lowered arterial blood pressure, and decreased peripheral resistance tend to reduce the work of the heart. According to the studies of Stewart, Crane, and Deitrick in cases of pernicious anemia, various opposing factors operate so that the work of the heart is not increased in spite of increased cardiac output. The total blood volume may be slightly reduced in anemia, although it is not lowered as much as is suggested by the fall in red cell volume, because plasma volume increases to some extent. Whether or not the work of the heart is increased in any case probably depends on additional factors and may differ from case to case. The fact that the heart has been found to be enlarged and hypertrophied in a number of cases of anemia has led to the assumption that the work of the heart has been increased. Cardiac hypertrophy in anemia has also been attributed to insufficient oxygen supply to the myocardium.

Increased oxygen utilization represents another means of physiologic adjustment to anemia. By this is meant the removal by the tissues of a greater proportion of the oxygen carried to them. Of the 18-21 volumes per cent of oxygen carried by the arterial blood, no more than 5.5 volumes per cent are ordinarily given up in the capillaries to the tissues. Were it not for increased oxygen utilization, cardiac output would have to reach even higher figures to maintain an adequate oxygen supply. The arteriovenous oxygen difference has been observed to fall in anemia to
between 19 and 41 cc. per liter, as compared with a normal average of 45 cc. per liter.

When the hemoglobin level of the blood is low, say about a third of normal, only 6 volumes per cent of oxygen are being carried by the blood. When anemia of this degree has developed, even if oxygen utilization is very greatly increased, the amount of oxygen available is seriously reduced. Furthermore, much of the oxygen load of the blood in such a case would be supplied to the tissues at a very low pressure—6 volumes per cent minus, for example, approximately 5 volumes per cent—which would result in anoxia, since this pressure is too low to be efficient. An increased circulation rate is beneficial here, because each unit of blood probably gives up a smaller proportion of its oxygen load, and thus oxygen is delivered to the tissues at a higher pressure than would otherwise be possible. Thus the arterio-venous oxygen difference, although it may at first be greater because of increased oxygen utilization, subsequently is reduced because of changes in circulation rate.

In anemia the vessels of the skin may be constricted, thus forcing a greater proportion of the blood through other regions. The oxygen consumption (basal metabolic rate) may be increased. Several investigators have noted a decreased vital capacity of the lungs. The reason for this is not evident, unless it is due to the presence of an increased amount of blood in the lungs coincident with an increased in the rate of blood flow.

The physiologic adjustment in anemia may be so efficient that a patient with only 1.5 Gm. of hemoglobin and 8 cc. volume of packed red cells per 100 cc. of blood, can manage to get out of bed and walk slowly about the room. I have seen a nurse permit such a patient to go by herself to the bathroom, and it was I who was shocked, rather than the patient, when I discovered how anemic the latter was.

It must be evident, however, that the physiologic adjustments resorted to by the anemic individual call for considerable encroachment on the reserves of the body. It is not surprising that such a patient may become short of breath on exertion or that symptoms of cardiac failure or of angina may appear. The edema found in association with anemia may be due to this cause, or to hypoproteinemia, or it may be independent of these. Venous pressure is not usually increased in cases of anemia unless congestive cardiac failure is present. According to the studies of Strauss and Fox, anemia per se, in some unexplained way, may be a factor conducive to water retention.

Much further study is required to determine whether the physiologic adjustments that have been described take place in all types of anemia.* Most of the studies here-tofore have been made in cases of pernicious anemia. Blumgart and his associates found that the velocity of the pulmonary blood flow was relatively slower in patients with anemia associated with carcinoma than in pernicious anemia at corresponding levels of hemoglobin. For this reason, they concluded, dyspnea, signs of

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* The excellent studies by Brannon, Merrill, Warren, and Stead (J. Clin. Investigation 30: 332, 1945) and by Sharpey-Schaefer (Lancet 2: 396, 1945), published since this paper was written, show clearly that increased cardiac output, increased oxygen utilization, and decreased peripheral resistance are present in cases of severe anemia.
congestive failure, peripheral edema, weakness, and cyanosis are frequently more pronounced in patients with carcinoma than would be expected on the basis of anemia, malnutrition, or toxicity. This is a problem for further investigation.

SICKLE CELL ANEMIA

There is one type of anemia that deserves special mention when the relation of the heart to anemia is being considered. This is sickle cell anemia. This strange disorder, seen— with certain rare exceptions— only in the Negro race, is characterized by the peculiar shape assumed by the red corpuscles when they are deprived of oxygen. The symptoms of this anemia are like those of any chronic anemia, but in addition the patients may suffer from attacks of severe pain in various parts of the body, especially in the extremities and about the joints. This complaint may appear following an upper respiratory infection, and may be accompanied by aching, headache, epistaxis, and pleuritic chest pain. Since fever is often associated with these attacks of pain, and leukocytosis is a characteristic part of the picture of this hemolytic type of anemia, the similarity to an acute inflammatory process is quite striking. The joints may be somewhat swollen and warm and the symptoms migratory. The condition has often been mistaken for rheumatic fever because of the peculiar manifestations relating to the heart. Even during quiescent states when no pain or fever was present, these patients have in error been regarded as having chronic valvular heart disease, particularly mitral stenosis. The first such case that came to my attention was that of a young Negro girl in whom the physical signs relating to the heart were so striking that several clinicians stated most emphatically that she must have rheumatic heart disease with mitral insufficiency and stenosis. At autopsy only a diffusely enlarged heart with normal valves and pericardium was found.

Cardiac enlargement has been observed in at least 76 per cent of cases of sickle cell anemia. The heart is enlarged both on the right and on the left; it may be globular in shape, or the pulmonary conus may be very prominent. Cardiac murmurs have been heard in at least 87 per cent of cases. The first sound at the apex is louder than normally, although it is not snapping in character. A systolic murmur, located best at the apex, is usually maximal early in systole. It may obscure the first heart sound. The second sound at the apex is often accentuated and a third heart sound is often heard early in diastole. Late in diastole there may be a murmur, and this presystolic murmur may blend with the first heart sound. A systolic murmur may be present in the pulmonic region and may be louder than the mitral murmur. The second pulmonic sound is usually accentuated and may be split. Diastolic murmurs at the base are rare.

In these patients pulsations may be prominent in the neck; the precordium is overactive—a phenomenon that is accentuated by a thin chest wall. A diffuse, wavy impulse may be readily visible in the fourth, fifth, and even sixth intercostal spaces to the left of the sternum. If the pulmonic conus is prominent, there may be a visible impulse and occasionally there is a bulge in the second and third interspaces to the left of the sternum. The point of maximum impulse is not well localized but is forceful and rolling, and there is a precordial lift. A diastolic tap may be felt in the
pulmonary area. A systolic thrill may be felt over the precordium and the vessels of the neck. The electrocardiographic changes noted have been similar to those found in other types of anemia.

It is sometimes impossible to distinguish sickle cell anemia from acute rheumatic fever, or its cardiac manifestations from those of rheumatic heart disease. In Negroes the presence of sickle cell anemia should be suspected and the blood should be examined for sickle cells. If these are found, the probability is that one is dealing with sickle cell anemia rather than with rheumatic fever. It is noteworthy that in the former the red corpuscles often do not settle out rapidly in the sedimentation test, probably because of their abnormal shape. Furthermore, careful inquiry may reveal that the pains in the extremities are localized more in the bones than in the joints. Roentgenograms may reveal characteristic changes in the bones. Finally, salicylate therapy is usually of little value in sickle cell anemia.

Unlike other types of anemia, sickle cell anemia is extremely chronic, the patient often going about with a red cell count of less than 2 million and rarely of more than 3 million, with little variation for eight, ten, or even fifteen years. One may ask whether the striking cardiac manifestations of sickle cell anemia may not represent in an extreme degree an exaggeration of the cardiovascular adjustments to anemia that we have described as occurring in anemia in general.

Besides this possibility there is another. It has been suggested that circulatory stasis in the small vessels of internal organs, muscles, and other tissues is the primary and the most perilous consequence of the sickle cell trait. Such stasis may be produced by the peculiar deformities of the red corpuscles and may put an added burden on the cardiovascular system. One of the many curious features of this disease is the extreme tortuosity of the blood vessels, which can often be observed in the ocular fundi. This may be due to a congenital anomaly; one may also ask whether it could be caused by circulatory stasis. Cases of sickle cell anemia have been described in which numerous disseminated occlusions of the small pulmonary arteries were found and cor pulmonale was produced. In these cases the small arteries were found to be lengthened, tortuous, hyalinized, and thrombotic—features revealing that these arteries had probably been subjected to severe, prolonged strain.

Whatever the mechanism may be, the heart in sickle cell anemia represents the extreme form of the "heart in anemia."

SUMMARY

The symptoms and signs referable to the cardiovascular system that are associated with anemia are discussed, and the physiologic adjustments to anemia that take place in the cardiovascular system are considered. The capacity for adjustment when anemia develops gradually, appears to be very great. The remarkable changes found in the cardiovascular system in cases of sickle cell anemia may be the result of adjustments to severe anemia of exceptional chronicity.

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THE CARDIOVASCULAR SYSTEM IN ANEMIA: WITH A NOTE ON THE
PARTICULAR ABNORMALITIES IN SICKLE CELL ANEMIA

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