Cardiovascular effects of anemia

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Anemia is the most common disease that may increase the cardiac output at rest. Chronic anemia in man usually increases the cardiac output when the hemoglobin level is 7 Gm. per 100 ml. of blood or less. Anemia not only decreases the oxygen-carrying capacity of the blood, but ordinarily decreases blood viscosity as well. Therefore, an understanding of the physiologic alterations of severe chronic anemia can clarify the mechanisms which control cardiac output. The clinical findings of a hyperkinetic state in anemia, although frequently quite striking, can be rapidly reversed by partial correction of the anemia in almost every instance. Circulatory congestion similar to that seen in congestive heart failure is an infrequent but serious complication of severe anemia. This may occur without pre-existing heart disease. There is no agreement as to whether this situation represents true congestive heart failure or "non-cardiac circulatory congestion." Therefore, we shall use the terms "congestive state" or "circulatory congestion" in referring to it.

Hemodynamics

Cardiac output. Studies in man have demonstrated that the cardiac output at rest is almost always elevated in severe chronic anemia, even when circulatory congestion supervenes. Exceptions occur in patients with underlying heart disease, patients with extremely low levels of physical activity (e.g., totally bedridden invalids) and patients with a hyperviscosity syndrome caused by a high serum globulin concentration, as in Waldenström's macroglobulinemia or multiple myeloma. The resting cardiac output is generally elevated when the hemoglobin level is below 7 Gm. per 100 ml. of blood and is usually even higher when the anemia is more severe (Fig. 1). In chronic anemia the increased cardiac output principally reflects a larger cardiac stroke volume, since tachycardia is frequently not found. At extremely low hemoglobin levels, below 3 Gm. per 100 ml. of blood, the cardiac output usually does not rise further, but almost always remains above normal. In patients with sickle cell anemia the negative correlation between cardiac output and hemoglobin level is not as clear-cut as in other types of anemia. In sickle cell anemia an elevated resting cardiac output may be found when the hemoglobin level is as much as 9 to 10 Gm. per 100 ml. of blood (Fig. 1).

The cardiac output response to exercise is...
typically greater than normal in anemia. Normal human subjects, during exercise, show an increase in cardiac output of 550 to 800 ml. per 100 ml. increase in oxygen consumption per minute. In patients with chronic anemia the increase of cardiac output with exercise is often from 1,000 to 1,500 ml., or greater, per 100 ml. increase in oxygen consumption per minute. The response to exercise is a more sensitive indicator of altered hemodynamics in anemia than is the level of resting cardiac output, since this exaggerated response is frequently found in patients with hemoglobin levels as high as 10 Gm. per 100 ml. of blood and normal resting cardiac outputs. The increase in cardiac output with exercise principally results from an increase in cardiac stroke volume; in contrast, in normal subjects the heart rate increases more than the stroke volume. In the congestive state of anemia, the increase in cardiac output during exercise is greater than normal, but not as great as in less anemic patients without congestion.

Circulation time. A short circulation time has been considered to be characteristic of the high output state associated with anemia. It is an easily elicited objective measurement which suggests a high cardiac output state. In two studies of patients with hemoglobin values ranging from 3.7 to 8.3 Gm. per 100 ml. of blood, the mean transit time of a bolus of dye injected into the venous side of the circulatory system was significantly shorter than after correction of the anemia. In individual patients with anemia, however, the circulation time is not always decreased when cardiac output is high. This apparent discrepancy may be the result of variations in venous tone or intravascular volume.

Central blood volume. Plasma volume, total blood volume, and central blood volume are not uniformly altered in chronic anemia. In general, plasma volume is slightly increased, whereas total blood volume and central blood volume are decreased. Since central blood volume usually falls to a lesser degree than total blood volume, the ratio of central to total blood volume is frequently increased. With the anemic congestive state, the change in central blood volume is variable, although it is usually increased. This point is of clinical interest, since transfusion of blood into anemic patients with circulatory congestion may have unpredictable effects. Transfusion may decrease central blood volume in some patients and increase it, with aggravation of pulmonary congestion, in others. Furthermore, the response cannot be predicted from the initial level of right atrial pressure. It is therefore advisable to correct anemia slowly, and if transfusion is needed, to use packed cells rather than whole blood and to monitor right atrial pressure during the transfusion.

Right heart pressures. Right atrial pressure usually remains normal in anemia, increasing only with circulatory congestion. Right ventricular and pulmonary arterial pressure are also normal in anemic patients without circulatory congestion. Pulmonary vascular resistance is decreased in anemia, since the increase in cardiac output is unaccompanied by an increase in mean pressure across the pulmonary vascular bed. The pulmonary vascular resistance decreases further during exercise, which in anemia is associated with a less than normal rise in pulmonary artery mean pressure. The pulmonary arterial wedge pressure, which in the absence of mitral stenosis is probably a fair representation of left ventricular filling pressure, was normal in three separate studies.
Left ventricular performance. Changes in the systemic circulation are similar to those in the pulmonary circulation. The systemic vascular resistance is decreased in proportion to the severity of the anemia. However, mean and diastolic arterial pressures fall only moderately, even at low hemoglobin levels. The systolic pressure is essentially unchanged, and the pulse pressure widens. As stated above, left ventricular end-diastolic pressure, measured indirectly, remains within normal limits. No studies of left ventricular pressure in anemic patients with circulatory congestion have been reported.

The stroke work of the left ventricle is moderately increased at rest in patients with hemoglobin levels below 7 Gm. per 100 ml. of blood. The increase in left ventricular stroke work with exercise is greater than normal in patients with anemia. Stroke work describes the work performed by the left ventricle in expelling a given volume of blood against a given systemic resistance. It is mathematically derived from the product of: (1) left ventricular stroke volume, which is increased in anemia; and (2) mean systemic arterial pressure (minus mean left atrial pressure), which is decreased. In anemia, therefore, the increase in the work of the left ventricle is caused by volume, as opposed to pressure, work. An additional small increase in left ventricular work is performed in accelerating the greater blood flow of anemia through a theoretically narrower aortic root. However, even under these conditions, the acceleration component probably remains a negligible part of the total work performed by the left ventricle.

The tension-time index per beat, which is an index of pressure work and rather closely related to myocardial oxygen consumption, except during beta-adrenergic stimulation or blockade, is significantly reduced in anemia. Left ventricular oxygen consumption can be estimated by measuring coronary blood flow and the coronary arteriovenous oxygen difference and calculating their product. In anemia, coronary flow increases in proportion to the increase in total cardiac output and possibly more so. In dogs with normovolemic dextran-induced anemia, coronary blood flow increased considerably while coronary sinus blood oxygen tension remained unchanged. In man, oxygen extraction by the myocardium is high (about 70 per cent) under normal conditions; the coronary arteriovenous oxygen difference, therefore, falls in essentially direct proportion to the hemoglobin level. The coronary arteriovenous oxygen difference decreases more than coronary flow increases, especially if the hemoglobin is below 3 Gm. per 100 ml. Thus, myocardial oxygen consumption appears to be decreased. In the face of increased left ventricular work, therefore, there would appear to be a very high level of myocardial efficiency. Unfortunately, this finding cannot be regarded as conclusive at this time because of the technical limitations of coronary flow measurements and the possibility that a significant amount of anaerobic metabolism may occur in anemic patients.

Regional blood flow. Cerebral blood flow is increased in patients with anemia. However, the increase in flow does not quite compensate for the decrease in the oxygen-carrying capacity of the blood, so that oxygen delivery to the brain is slightly reduced. Cerebral oxygen consumption is also decreased. In dogs with hypervolemic and normovolemic dextran-induced anemia, the blood flow through the carotid arteries increased in the same proportion as the cardiac output. In the same study, femoral arterial blood flow also increased in proportion to the increase in cardiac output. Hepatic blood flow was increased in patients with anemia in one study. Studies of the influence of hematocrit on renal blood flow have produced inconsistent results. Early investigations in man suggested that renal blood flow, measured indirectly, was diminished in anemia. In addition, excretion of a sodium load was found to be impaired in patients with anemia. This had been suggested as a possible explanation for the moderate edema occasionally found in anemia. However, more recent studies have demonstrated different effects of anemia on renal blood flow and function. Schrier and Earley, in their study using dogs, found that normovolemic exchange anemia resulted in an increase in renal blood flow (measured by clearance techniques) and a more rapid excretion of sodium. In another study of dogs with
hypovolemic or normovolemic dextran anemia, renal blood flow was measured directly with an electromagnetic flowmeter. In these anemic dogs, renal blood flow increased considerably. This large increase is significant, since autoregulation should tend to minimize changes in blood flow.

**Compensatory mechanisms in anemia**

The major physiologic consequence of anemia is a reduced oxygen-carrying capacity of the blood. The resultant tissue hypoxia evokes several compensatory mechanisms. One such mechanism is peripheral vascular dilation, which is associated with increased blood flow to the periphery. Another mechanism is increased tissue extraction of oxygen from the blood. This is accomplished, at least in part, by a shift to the right of the oxyhemoglobin dissociation curve, which allows more oxygen to be unloaded from the erythrocyte at any given blood oxygen tension. Recently, this phenomenon has been shown to be related to increased concentrations of organic phosphates, especially 2,3-diphosphoglycerate, within the red blood cell. This rightward shift probably occurs in severe anemia of any cause, but is more pronounced in sickle cell anemia. The fact that the systemic arteriovenous oxygen difference is decreased in anemia (3 volumes per 100 ml. of blood as opposed to 4 to 5 volumes per 100 ml. of blood in normal subjects), indicates that the increased tissue extraction of oxygen is only of secondary importance.

In anemic patients, the most important mechanism in maintaining an adequate oxygen supply to the tissues is an increase in cardiac output. As stated previously, cardiac output is usually increased in patients with chronic anemia when the hemoglobin is approximately 7 Gm. per 100 ml. of blood or less. In general, the cardiac output increases in roughly linear fashion with increasing severity of the anemia (Fig. 1). At very low hemoglobin levels, when oxygen extraction has reached a near-maximum, an increased cardiac output is the only means of insuring adequate tissue oxygenation. The increase in cardiac output is not completely compensatory, since total oxygen transport, that is, the product of cardiac output and arterial oxygen content, is somewhat less than normal in anemia. When the hemoglobin falls to below 2 or 3 Gm. per 100 ml. of blood, the leveling off of the cardiac output (Fig. 1) and the inability of tissue extraction of oxygen to increase any further must lead to significant tissue hypoxia. With this degree of anemia, circulatory congestion and angina pectoris may occur, thus emphasizing the sensitivity of the myocardium to chronic hypoxia. In dogs, Eckstein demonstrated that severe anemia alone can stimulate the growth of coronary artery collateral circulation.

**Mechanisms responsible for the increased cardiac output of anemia**

The mechanism of the increased cardiac output in chronic anemia has not been clearly defined, although several explanations have been proposed. Tachycardia can be dismissed as an important factor, since it is frequently absent in chronic anemia. An increase in cardiac stroke volume, on the other hand, does appear to be important. Stroke volume is usually increased in chronic anemia, even when the heart rate is rapid. Cardiac stroke volume also increases with exercise, unlike the situation in normal subjects, in which tachycardia is mainly responsible for the increase in cardiac output. An explanation for the increased stroke volume might be found by considering alterations in ventricular preload and afterload and myocardial contractility in anemia.

**Preload.** Ventricular preload is determined by the ventricular end-diastolic fiber length and is usually estimated by measuring ventricular end-diastolic pressure (or atrial pressure) or end-diastolic volume. Either end-diastolic pressure or volume, or both, should be increased if a change in preload is responsible for the increased stroke volume. However, since the relation between these two variables is influenced by ventricular wall compliance, end-diastolic pressure alone is an unsatisfactory measure of preload. Unfortunately, only the atrial pressure has been well studied in patients with anemia. It has been found to be normal, except in patients with anemia and circulatory congestion.

There are no reported measurements of
ventricular volume in patients with anemia. However, total blood volume and central blood volume, both of which strongly influence ventricular end-diastolic volume, were found to be unchanged, or more often, diminished in anemia. The production of hypovolemic and hypervolemic anemia in dogs also demonstrated that an expanded blood volume was not essential to the increased cardiac output. In a study in which isovolemic dextran-exchange anemia was produced in dogs, ventricular end-diastolic volume increased slightly, although the change was not statistically significant.

**Myocardial contractility.** Myocardial contractility is measured by the velocity of muscle shortening at a given end-diastolic volume and tension. Studies of both open and closed chest dogs suggest that an increase in myocardial contractility accompanies the high stroke volume in dextran-exchange anemia. The mechanism by which ventricular contractility is increased is not clear. In the experimental animal, perfusion of the aortic and carotid chemoreceptors with hypoxic blood led to an increase in myocardial contractility in one study. In another study, however, cardiac stroke volume increased during anemia without chemoreceptor stimulation. In still other studies, a rise in cardiac stroke volume in anemic dogs was not prevented by beta-adrenergic receptor blockade or by cardiac denervation. Available evidence, therefore, suggests that the sympathetic nervous system is not essential for increasing myocardial contractility or stroke volume in anemia, although it may have some additive effect.

**Afterload.** The major determinants of ventricular afterload are vascular resistance and blood viscosity. Vascular resistance in turn depends on the caliber of the peripheral vessels and the presence or absence of arteriovenous shunts. Peripheral arteriovenous shunting in chronic anemia has not been examined, although it has been suggested that peripheral shunting may occur in sickle cell anemia and that this may be responsible for the increased cardiac output.

The relation between peripheral vasodilation and the high output state has received considerable attention. A decrease of systemic vascular resistance accompanies the increased cardiac output found in anemia. Duke and Abelmann recently suggested that a fall in systemic vascular resistance is of primary importance in producing the high cardiac output. They infused methoxamine, a powerful alpha-adrenergic receptor stimulating agent which acts predominantly on the peripheral vascular bed, into patients with anemia. In normal subjects, infusion of methoxamine increases peripheral resistance and causes reflex bradycardia. The level of cardiac output is maintained by an increase in stroke volume. In 6 of the 7 anemic patients studied by Duke and Abelmann, methoxamine infusion increased peripheral vascular resistance and decreased cardiac output, with but a small rise in stroke volume. In another study, when atropine was administered concurrently with methoxamine in order to abolish the reflex bradycardia, cardiac stroke volume actually fell in patients with anemia. These observations suggest that decreased peripheral vascular resistance plays a central role in the high output state of anemia.

If peripheral vasodilation is indeed of central importance, how is it mediated? Local tissue hypoxia, lactic acidemia, and an accumulation of substances such as adenosine and bradykinin have all been suggested as factors that increase cardiac output by decreasing peripheral vascular resistance. Since they result from inadequate tissue oxygenation, it is tempting to assign an important function to one or more of them in anemia. A positive correlation between the severity of anemia and the lactate : pyruvate ratio (but not the lactate concentration) has been noted in the experimental animal. However, no study of the relation between any of these factors and cardiac output in patients with anemia has been made, and their role remains a matter of speculation.

The possibility that a humoral factor may be responsible for the increased cardiac output was suggested by one study in dogs. In that study, transfusion of blood from an anemic dog into normal animals increased the cardiac output in some of the recipients. Clinical support for the importance of a humoral factor is found in the observation that cardiac output does not
fall to normal immediately following correction of the anemia in many patients. However, the presence of a humoral factor has not, to our knowledge, been confirmed by studies in man.

A decrease in blood viscosity has been considered by some investigators to be of central importance in producing the increase in cardiac output. The most important determinant of whole blood viscosity is the ratio of red cell volume to plasma volume. The magnitude of the fall in effective viscosity associated with a given fall in hematocrit is not easily predictable, however, since blood is a non-Newtonian fluid, that is, its observed viscosity depends on the rate of shear (or flow). A rough impression can be obtained from one series of 8 patients with chronic anemia, in which observed viscosity (utilizing a rotational viscometer) fell 39 per cent with a 44 per cent fall in hematocrit, at a shear rate of 60 revolutions per minute. Even when the in vitro blood viscosity is known, its hemodynamic effects are uncertain, since the effective viscosity is dependent on the caliber of the vessels being perfused, as well as the flow rate. Despite these difficulties in interpretation, the influence of decreased blood viscosity on cardiac output has been documented in several studies.

In the dog heart-lung preparation, Fowler and Holmes decreased blood viscosity with exchange transfusions of either dextran or red blood cells suspended in Krebs solution. Although similar decreases in blood viscosity were produced, anemia accompanied the transfusion of dextran, whereas it did not occur with exchange of red cells. Despite the large differences in arterial blood oxygen content between them, the two groups of animals showed quite similar increases in cardiac output. Murray and Escobar demonstrated the importance of blood viscosity changes in the intact animal. They decreased the oxygen-carrying capacity in dogs by exchange transfusion with either methemoglobinemic blood or dextran. The cardiac output did not rise with transfusion of the former, but it did rise significantly with dextran exchange, which, of course, decreased blood viscosity. A somewhat different approach was utilized by Weber and associates in human subjects. They found the cardiac output to be significantly less than normal in patients with polycythemia vera in whom the blood volume, but not the hematocrit, had been reduced to normal by treatment with P. These studies not only confirm an inverse correlation between blood viscosity and cardiac output, but also strongly suggest that viscosity changes may affect cardiac output, probably by altering peripheral vascular resistance.

In summary: (1) Chronic anemia tends to be associated with an increase in cardiac stroke volume; (2) an increase in ventricular filling pressure or in total blood volume is not essential for this increase in stroke volume; (3) an intact beta-adrenergic receptor system is not essential to the cardiac output increase of chronic anemia; and (4) a decrease in afterload, secondary to decreased peripheral resistance and/or decreased blood viscosity, is probably a major factor.

Clinical aspects

Symptoms. In patients with chronic anemia, cardiovascular manifestations usually appear when the hemoglobin falls below 7 Gm. per 100 ml. of blood, although exercise may elicit symptoms in some patients with milder anemia. The most common complaints are fatigue and dyspnea on exertion, although at rest many patients with very low hemoglobin levels may remain remarkably comfortable. Palpitation and slight ankle edema are less frequent complaints. Occasionally, mental confusion may be prominent in elderly patients with severe anemia. Orthopnea, dyspnea at rest, and extensive edema are usually found only when the anemia is severe enough to produce circulatory congestion. Angina pectoris occurs infrequently in anemic patients, probably because of the very efficient extraction of oxygen from the blood by the myocardium and the decreased myocardial oxygen consumption that occurs in anemia. There is, in addition, experimental evidence that severe chronic anemia in the dog stimulates the growth of coronary collateral vessels. When angina pectoris does occur, it is usually associated with underlying coronary artery disease, although a
few anemic patients with angina and normal coronary arteries at autopsy have been reported.63

Physical findings. Physical findings not related to the cardiovascular system are sparse in anemia. The skin is usually warm; there is pallor of the skin, nailbeds, and mucous membranes and occasionally slight ankle edema is present. The arterial pulse, although not necessarily rapid, is bounding in character, reflecting a somewhat widened pulse pressure. The cardiac examination is more rewarding in terms of positive physical findings (Fig. 2). On palpation, the precordium is very active. Enlargement of the heart may be indicated by leftward displacement of the apical impulse. On cardiac auscultation, the first and second heart sounds tend to be louder than usual, but are ordinarily otherwise normal. In patients with sickle cell anemia there may be audible expiratory splitting of the second sound, with a loud pulmonic component.15 A gallop rhythm, even in the absence of circulatory congestion, is commonly found in anemia. Both $S_2$64 and $S_4$65 gallops occur. In a recent study the $S_4$ gallop was heard twice as often as the $S_2$.66

A systolic ejection murmur is the most common murmur in patients with anemia. The pitch, intensity, and location of this murmur are quite variable, although typically it is low-pitched66 and not over grade 3 (using a 1-6 grading system) in intensity. The murmur is usually heard best in the second left intercostal space or along the lower left sternal border, although in one large series64 it was heard best at the apex. An accompanying precordial thrill is uncommon in anemia. Mid-diastolic rumbling murmurs may be heard in patients with sickle cell anemia. They probably are caused by increased blood flow through the mitral and/or tricuspid valves. Diastolic blowing murmurs attributable to semilunar valve insufficiency are very uncommon in anemia. A diastolic blowing murmur is usually associated with underlying aortic valve disease, although there have been a few cases in which no heart disease was found at autopsy.67 It is likely that in the great majority of cases, anemia merely accentuates a diastolic blowing murmur that is otherwise too faint to be heard easily. We have occasionally observed an early diastolic blowing murmur in uremic patients with hypertension and severe anemia, in whom there was no other clinical, or autopsy, evidence of aortic valvular disease, and in those patients with sickle cell anemia who have pulmonary hypertension and pulmonary valvular insufficiency.

Examination of the large arteries and veins may provide additional auscultatory signs of anemia. There may be loud systolic bruises over the carotid and subclavian arteries.68,69 The cervical (jugular) venous hum is frequently present in healthy children70,71 and is less common in normal adults. This murmur is more common, and more intense, in patients (including

Fig. 2. Phonocardiogram of a 44-year-old woman with severe chronic anemia (hemoglobin 3.7 Gm.) and no underlying heart disease. A venous hum is demonstrated in the recording obtained from the right side of the neck (upper panel). The hum increases in intensity just before the second heart sound (A) and reaches maximum intensity in early diastole. A systolic ejection murmur is present in the tricuspid area tracing. The mitral area record (lower panel) demonstrates prominent third and fourth heart sound gallops. CPS = Cycles per second; $S_3$ = third heart sound gallop; $S_4$ = fourth heart sound gallop.
adults) with severe anemia (Fig. 2). When a cervical venous hum is heard in a recumbent adult, anemia, thyrotoxicosis, or another high output state is suggested. It is one of the characteristic signs of the high output state associated with anemia, and it occurred in 82 per cent of adult patients in a recent series. The venous hum is a continuous murmur with diastolic accentuation that is heard over the neck, in the supraclavicular area, and occasionally over the upper precordium. It is best appreciated with the patient in the sitting position, his chin turned to the contralateral side. It is easily obliterated by light pressure on the internal jugular vein. Rarely, a continuous venous hum may also be heard over the femoral veins. Other findings are the Duroziez' sign and pistol shot femoral pulses, which presumably reflect the peripheral vasodilation of anemia. In anemia, the Duroziez' sign is elicited by compressing the artery proximal to the point of auscultation, rather than distal to it, as in aortic valvular insufficiency.

Electrocardiographic findings. There are no characteristic electrocardiographic changes in anemia. Although early reports described a decrease in QRS amplitude, T-wave flattening, and minor degrees of atrioventricular conduction disturbance, these have not been observed in more recent series. Later studies reported frequent non-specific ST-T-wave changes. It is not certain, however, that these changes are more common in anemic patients than in comparable patients without anemia. Electrocardiographic changes suggestive of right atrial enlargement and/or right ventricular hypertrophy were found in a small number of patients with sickle cell anemia in one series of consecutive hospital admissions. However, in a series of patients with sickle cell anemia selected because they had clinical evidence of pulmonary infarctions and pulmonary hypertension, the electrocardiograms were usually normal.

Roentgenographic findings. The heart was enlarged on chest roentgenogram in from 33 per cent to 67 per cent of patients with severe anemia (hemoglobin less than 7.5 Gm. per 100 ml.). In some series, cardiomegaly occurred more often in patients with very low hemoglobin levels and in those who had prolonged anemia. In another report, cardiac enlargement and the duration of anemia were unrelated. An enlarged heart may be more common in anemic patients more than 50 years old. Whether this reflects underlying heart disease or impairment of compensatory mechanisms is not known. Cardiac enlargement is more common in sickle cell anemia than in other kinds of anemia, occurring in all patients in one series. When the heart is enlarged, it tends to return to normal within a few weeks after correction of the anemia, except in patients with sickle cell anemia. Roentgenographically, the lung fields remain clear, except in some patients with circulatory congestion.

Differential diagnosis. The diverse, and often quite striking, auscultatory manifestations of anemia may easily give rise to mistaken diagnoses of organic heart disease. Aortic stenosis, for example, may be suggested by a rough systolic ejection murmur and carotid bruits. The erroneous diagnosis of aortic regurgitation may be made when a venous hum, which is accentuated in diastole, is heard over the upper precordium and there are peripheral signs of vasodilation and increased pulse pressure. In patients with sickle cell anemia, mitral stenosis may be suspected because of a loud first heart sound, a mid-diastolic rumbling murmur, and an S4 gallop which may be misinterpreted as a pre-systolic murmur. It should be emphasized that all these auscultatory phenomena can occur without underlying heart disease and that all of them may disappear when the anemia has been corrected.

The symptoms of severe anemia, namely, fatigue, dyspnea, and ankle edema, may suggest an erroneous diagnosis of heart disease with heart failure. In patients with sickle cell anemia, the roentgenographic demonstration of left atrial enlargement and prominent pulmonary arteries may reinforce the mistaken clinical impression of mitral stenosis.

Sickle cell anemia. The cardiovascular alterations in sickle cell anemia often vary in kind and degree from those found in other types of anemia. The chronicity of the anemia, the increased viscosity of the red blood cells, the microthrombi and tissue
infarctions, the characteristic oxygen undersaturation of arterial blood, and the more pronounced rightward shift of the oxyhemoglobin dissociation curve probably influence the response of the cardiovascular system to the anemic state. The auscultatory findings associated with anemia tend to be present in sickle cell anemia patients at a higher hemoglobin level than in other anemic patients. The cardiac output is elevated with less severe anemia in patients with sickle cell anemia (Fig. 1).

Pulmonary hypertension, presumably caused by microthrombi, is found in a small percentage of patients with sickle cell anemia. In these patients, in addition to the various murmurs characteristic of anemia, clinical findings related to pulmonary hypertension may be present. In this case, a right ventricular parasternal lifting impulse and the pulmonic component of the second heart sound are palpable. The second heart sound may show audible expiratory splitting with increased intensity of the pulmonic component. These changes, taken together with the occasional findings of expansile pulmonary arteries on fluoroscopy, may lead to the erroneous diagnosis of atrial septal defect. Occasionally, right ventricular gallops and the murmur of pulmonary valve insufficiency are heard. It should be stressed that pulmonary hypertension occurs in only a small minority of patients with sickle cell anemia, even though cardiac enlargement is present in 60 per cent to 100 per cent of patients with sickle cell anemia and prominent pulmonary artery segments are occasionally demonstrated by chest roentgenogram. In the great majority of patients, there is no clinical evidence of cor pulmonale and resting pulmonary artery pressure is within normal limits.

Other hemoglobinopathies are associated with circulatory abnormalities, although these are not as prominent as in sickle cell anemia. The occurrence of splenic infarction in patients with the sickle cell trait, who fly at high altitudes in unpressurized aircraft, is well documented. In autopsy studies, massive intravascular sickling was felt to be the major cause of death in some patients with the sickle cell trait and a significant contributing factor to the death of others. Hemoglobin S-C disease is associated with a clinical picture similar to that of sickle cell anemia. In hemoglobin S-C disease, however, the anemia is less severe, painful crises are less frequent, and cardiac abnormalities are unusual. As in patients with the sickle cell trait, infarction of the spleen at high altitudes and occasionally fatal extensive intravascular sickling may occur in patients with S-C hemoglobin. In addition, fat embolism has been reported as a cause of death in patients with hemoglobin S-C disease. Another hemoglobinopathy, thalassemia major, was associated with an increased prevalence of pericarditis diagnosed at autopsy. In that series, all of the patients had survived for relatively long periods and had evidence of iron overload involving the heart as well as other organs. Hemochromatosis involving the heart also may occur in association with aplastic and refractory anemias.

Circulatory congestion. A small number of patients with very severe chronic anemia (usually with less than 5 Gm. of hemoglobin per 100 ml. of blood) and no underlying heart disease develop clinical features usually associated with congestive heart failure; that is, they have elevated systemic venous pressure with distended neck veins, hepatomegaly, and significant peripheral edema. Despite the clinical similarities, however, at least some patients in this group display hemodynamic differences from patients with congestive failure associated with heart disease. They may have a normal or decreased total blood volume, a short circulation time, and an elevated resting cardiac output. Their cardiac output response to exercise, while less than that of anemic patients without circulatory congestion, is greater than normal. Eichna observed that in patients without underlying heart disease, the clinical picture of circulatory congestion was reversed when the anemia was corrected. Intravenous and oral digoxin were ineffective in lowering the systemic venous pressure. He suggested that the term "non-cardiac circulatory congestion" was appropriate in describing such patients with anemia.

However, there is far from total agreement with this concept. The poor tolerance of some of these patients to the intravenous administration of very small volumes
of fluid suggests that true myocardial failure contributes to the clinical picture. The effect of anemia upon cardiac function was studied in the dog heart-lung preparation by employing dextran exchange to lower the hematocrit to 2 to 7 per cent. This degree of anemia consistently raised atrial pressures and decreased cardiac output from the elevated values that had been present at lesser degrees of anemia. In these studies, the administration of intravenous ouabain was followed by a return of the atrial pressure to normal and by an increase in cardiac output. It would appear that at some very low hemoglobin level, compensatory mechanisms may not be able to overcome myocardial hypoxia, and myocardial failure may occur. This is probably not the sole factor in producing the congestive state associated with severe anemia. Other factors, such as the response of the coronary circulation, the role of peripheral venoconstriction, and the possibility of impaired ventricular function, remain to be evaluated.

REFERENCES


