THE RELATIONSHIP OF THE BLOOD, the most easily analyzed organ of the body, to the brain, the most remote and the focus of neurologists' attention, is strikingly apparent in cerebrovascular disease where thrombosis, atherosclerotic obstruction of vessels, and consequent failure to transport a constant supply of oxygen demonstrate the dependence of the nervous system on a properly functioning circulation. Frequently overlooked in our emphasis on platelets, coagulation, and vascular endothelium, however, is the importance of the red blood cell, the keystone of the interaction between blood and brain. Without normally functioning erythrocytes, a constant and sufficient supply of oxygen cannot be provided to threatened neurons rendered ischemic by underlying disease processes. Furthermore, primary red blood cell abnormalities, most notably changes in concentration (polycythemia or anemia) or structural alterations in the hemoglobin molecule, may themselves be the cause of cerebrovascular disease. As a result, therapy of cerebral ischemia may be aimed at altering the concentration or properties of the red blood cell in order to improve oxygen delivery. This paper will discuss the pathophysiology of red blood cell disorders, their clinical aspects and therapy in the context of cerebrovascular disease.

Red Blood Cell Pathophysiology

The delivery of oxygen to tissue depends on three factors: 1) The functional integrity of the pulmonary, cardiac, and vascular system and the tissue being supplied, 2) The quantity and quality of the hemoglobin molecule and the binding of hemoglobin and oxygen, and 3) the flow characteristics of the blood (rheology). The first factor, i.e., the integrity of organ systems beside the blood is beyond the scope of this review.

Hemoglobin, Oxygen Binding, and Red Blood Cell Structure

The structure and biochemistry of the hemoglobin molecule is now well understood. Normal hemoglobin (HbA) consists of two alpha and two beta globin chains bound to an iron-containing heme molecule, forming a tetramer. Oxygen reversibly binds to this complex converting Fe+++ to Fe++, but the binding and release of the O2 molecule is highly dependent on the intracellular environment and the structure of the hemoglobin molecule. The well-known sigmoid shaped curve of oxygen partial pressure and oxygen content is shifted to the right (i.e., reduced affinity and therefore augmented release of O2 to tissue) by acidosis (fig. 1). Red blood cell ATP and 2, 3 diphosphoglycerate (2,3 DPG) also affects this curve by binding to deoxyhemoglobin under hypoxemic and anemic conditions also resulting in a shift of the curve to the right. Thus, when tissue is ischemic and local pH and O2 content are low, compensatory mechanisms in erythrocytes favor enhanced release of O2 from hemoglobin.

Many amino acid substitutions can occur along the globin chain resulting in altered stoichiometry and oxygen binding. Some, such as in methemoglobinemia, merely result in an inability to shift the Hb-O2 dissociation curve but do not cause altered erythrocyte structure. Secondary polycythemia may occur due to reduced oxygen release per red cell. More commonly, these substitutions occur at crucial sites of heme binding to globin resulting in dissociation of the tetramer. Denaturation of the isolated globin chains in turn may result in precipitation into the cytosol as Heinz bodies causing alteration of red cell shape, splenic trapping of the abnormal cells, and hemolytic anemia. A similar mechanism occurs in the thalassemias, where there is imbalanced synthesis of part of the alpha or beta globin chains, and in glucose 6 phosphate dehydrogenase (G6PD) deficiency. In this latter disorder, there is reduced production of red cell NADPH, a key intermediate contributing to the cell's reducing capacity. This exposes the hemoglobin to oxidation and precipitation, especially in the presence of certain drugs. No cerebrovascular complications of these disorders have been reported except those related to excessive blood transfusion and consequent coagulopathy, and the reader is referred to standard hemotology texts for a more detailed description.

The hemoglobinopathy most commonly associated with cerebrovascular disorders is sickle cell disease where a point mutation results in a globin beta chain valine substitution. This substitution significantly lowers the solubility of deoxy hemoglobin S such that it is prone to aggregation. Under relative hypoxic or acidic conditions such as normally occurs in the venous circulation, these aggregates lead to polymerization of
hemoglobin tetrmeric into a rigid gel resulting in a drastic change in red cell shape and deformability. The consequent heightened whole blood viscosity and reduced flow results in further tissue hypoxia and acidosis causing even more sickling, the well-known cycle leading to sickle crisis. Polymerization reverses when Hb is oxygenated but some cells become irreversibly sickled. Even in cells not irreversibly sickled, internal red cell viscosity increases, and deformability decreases resulting in sludging and hemolysis.

Homozygotes (HbSS) represent 0.03 to 0.16% of the Black population in this country. In this condition, 80 to 98% of the hemoglobin contains the abnormal beta globin chains with the remainder fetal hemoglobin (HbF). Those patients with relatively high content of HbF may therefore have a less severe form of disease. Heterozygotes (HbSA) represent 8.5% of the U.S. Black population and have variable amount of normal beta chains. If a heterozygote gets the gene for HbS from one parent, and another abnormal gene such as that for HbC from the other, syndromes of intermediate severity such as HbSC disease may result. The exact prevalence of HbSC is unknown but is estimated to be between 0.02 and 0.21% of Blacks in this country.

Abnormalities in the red blood cell membrane may result in hemolysis and occasionally produce cerebrovascular symptoms. Spherocytosis, an autosomal dominant condition marked by reduced erythrocyte deformability and hypersplenism, and immune hemolytic anemia (idiopathic or secondary to underlying blood dyscrasias, connective tissue disease, infection, or drugs) are classic examples but have not been associated with cerebrovascular disease. Paroxysmal nocturnal hemoglobinuria results from dysplastic marrow and the production of an abnormal population of red cells, white cells, and platelets. These cells demonstrate enhanced complement fixation resulting in rupture of the erythrocyte membrane, hemolytic anemia, hemoglobinuria, platelet aggregation, and venous thrombosis.

Rheology

As recently reviewed by Wood et al in this forum, circulation in the brain is governed by certain rheological principles which demonstrate the central role of whole blood viscosity in the determination of cerebral blood flow (CBF). The first and most important of these principles is embodied in the Hagen-Poiseuille equation,

$$Q = \frac{\Delta P \pi r^4}{8L \eta}$$

where Q is blood flow, $\Delta P$ is pressure gradient, r is vessel radius, L is vessel length, and $\eta$ is blood viscosity. Whole blood viscosity is chiefly determined by the red blood cell. Merrill introduced the term yield shear stress (YSS), essentially the viscosity or resistance to the initiation of movement in a stationary column of blood:

$$YSS = 13.5 \times 10^{-6} C_f^2 (Hct - 6)$$

where $C_f$ is the fibrinogen concentration in gm%, and Hct is the hematocrit. Thus the red cell mass or Hct is the overriding determinant of YSS, and has been shown to correlate inversely with CBF in numerous studies.

Understanding these principles of oxygen delivery and rheology, what is the optimal hematocrit for oxygen delivery to ischemic brain? Gottstein has studied cerebral metabolic rate of oxygen (CMRO2) and Messmer has calculated oxygen delivery to various tissues over a wide range of Hct, and a parabolic relationship was derived demonstrating maximal O2 delivery at Hct between 30 and 33%, significantly lower than the normal Hct range at sea level (36-47%) (fig. 2). In patients with normal cardiac reserve, reduction in oxygen carrying capacity by lowering Hct to 30-33% is more than offset by a concomi
tant rise in cardiac output and CBF resulting from lowered viscosity and vascular resistance in the brain. These relationships between Hct and CMRO2 were derived in normal brain, and may not hold true in cerebral ischemia where Hb-O2 binding is altered. However, tissue hypoxia and acidosis should enhance the release of oxygen by red cells in ischemic regions so that oxygen availability should be no less at a given Hct in ischemic compared to normal brain. Nevertheless, confirmation of enhanced oxygen delivery is urgently needed as therapeutic hemodilution protocols are undertaken in patients who often have impaired cardiac reserve. Studies of oxygen metabolism by positron emission tomography would be a logical means of obtaining this information.

The deformability of the erythrocyte is another important determinant of whole blood viscosity, particularly in the microcirculation where capillary diameter (4–6u) is in fact smaller than red blood cell diameter (8u). This mismatch necessitates deformation of the red cell and contributes to the inversion phenomenon describing the increased viscosity seen at the capillary level compared to larger conductance vessels. The normal biconcave disc shaped erythrocyte is 2u in width and 8u in diameter, but because of its deformability can traverse a 14 u long channel that is only 2.8u wide, and can squeeze through small 0.5u openings between cells. Normal deformability of the red blood cell depends on normal hemoglobin structure as well as adequate ATP stores to maintain and alter cell shape and to actively extrude calcium which if allowed into the erythrocyte can cause gelation of hemoglobin and contraction of actomyosin-like proteins in the red cell membrane.

Primary Red Blood Cell Disorders

These physiologic principles (vide supra) suggest several mechanisms by which primary red cell disorders might cause or aggravate cerebral ischemia by adversely affecting oxygen delivery or CBF. Hemoglobinopathies limiting the binding and delivery of O2 and causing altered erythrocyte shape and heightened viscosity, and anemia or polycythemia which would adversely affect red cell deformability further aggravating tissue injury.

Sickle Cell Anemia (HbSS)

This is the most common hemoglobinopathy, and 8–17% of patients homozygous for HbS will have cerebrovascular complications, 50–70% of these recurrent. This is compared to a stroke incidence of 2–5% in HbSC, and 1.5–2% in HbSA and normal (HbAA) Blacks. Seven percent of all cases of infantile hemiplegia are due to HbSS, and the mean age of all stroke patients with HbSS is 7.7 years. Seventy-five percent of strokes are infarcts and the remainder hemorrhages, although intracerebral hemorrhage is more prevalent in adult HbSS stroke patients. Subarachnoid hemorrhage only accounts for 1–2% and many of these are probably due to aneurysmal rupture unrelated to HbSS.

Why are most sicklers free of stroke? Evidence indicates that cerebrovascular complications occur in patients with the most severe disease since the average number of crises in stroke patients is 18.6% versus 9.3% in patients without neurologic symptoms. Furthermore, there is a higher incidence of infection and cardiomegaly in sicklers with stroke, again indicating more severe disease.

Strokes occur when tissue hypoxia and acidosis result in hemoglobin polymerization, sickling, occlusion of small vessels, and stasis. Although these changes occur in the microcirculation, the most common arteriographic finding in HbSS stroke patients is internal carotid artery narrowing and occlusion which may ultimately lead to a Moya Moya pattern. Most likely, obstructed flow in the vasa vasorum by sickled cells leads to ischemia of the carotid artery wall, intimal proliferation, and occlusion. This scenario could also lead to necrosis of the vessel wall and may be responsible for some hemorrhages in HbSS patients. It is important to remember that arteriography is fraught with risk in HbSS patients but can be done safely if the percentage of HbS is reduced below 20% by exchange transfusion.

Strokes often occur heralded by other signs of a vaso-occlusive sickle crisis including fever and abdominal, bone, or chest pain. Meningismus and seizures may develop, and besides hemiplegia due to carotid occlusion, symptoms may occur due to infarction in the brain stem and spinal cord. Central retinal artery occlusion, retinal vascular proliferation, and retinal and vitreous hemorrhages are frequently seen. In the venous circulation, dural sinus thrombosis may result in increased intracranial pressure, obtundation, seizures, as well as focal neurologic signs from infarct or hemorrhage. A rare occurrence is fat embolism to the brain following bone marrow infarction.

While the diagnosis of HbSS is usually obvious in patients with this condition having stroke, HbSC disease may remain asymptomatic until adulthood and may cause strokes unheralded by other symptoms of sickle crisis in an age group where the prevalence of atherosclerosis might dull the clinician into ascribing the stroke to thromboembolism. A striking example was a 58-year-old woman who suffered a left and then a right frontal subcortical infarct 1 year apart. Arteriography and cardiac evaluation were unremarkable although the patient did worsen slightly after her arteriogram. There were no striking stroke risk factors and CBC and smear were reported as normal. She was treated with platelet antiaggregant drugs and then warfarin but despite these therapies over the next 3 years went on to have a left parietal and then brain stem infarct manifest by palatal myoclonus (fig. 3). HbSC disease was not diagnosed until sickle cells were seen in a leptomeningeal biopsy performed to exclude arteritis.
Stroke therapy in HbSS should include the usual measures employed in all patients with stroke, but particular attention should be placed on correcting underlying tissue hypoxia and acidosis by hydration, reduction of fever and treatment of underlying infection. Anticonvulsant therapy is often needed to prevent seizures. Unfortunately, anticoagulation with heparin or warfarin has not been shown to reduce the number or severity of strokes. Dextran and platelet antiaggregant therapy may be useful but are as yet of unproven value. More specific therapy for HbSS related stroke includes lowering the relative quantity of HbS by exchange transfusion and efforts to alter the red cell environment leading to sickling.

Exchange transfusion (XT) to achieve a relative HbS content of 20% is presently the mainstay of stroke prevention. In patients who already have suffered a stroke, the expected recurrence is above 60%, 80% of these within 3 years. In one series, chronic XT therapy reduced the incidence of recurrent stroke to 10% and regression of arteriographic abnormalities and increased CBF were also demonstrated in some patients although progression of the Moya Moya pattern has been documented despite XT by other observers. Improved microcirculatory flow has been demonstrated after XT by laser doppler velocimetry and this may be a useful technique for assessing therapy and discovering perturbations in the microcirculatory bed. Since most stroke recurrences occur within 2 years, a 1–2 year course of XT was evaluated in the hope that complications of prolonged transfusion therapy including hemosiderosis, hepatitis, transfusion reaction, and AIDS, might be avoided. However, when XT was stopped after 1–2 years, 7 of 10 patients suffered a stroke over the next 11 months indicating that XT must be long term to effectively prevent stroke recurrence.

Other methods to lower the quantity of HbS are under investigation. Gene manipulation to increase the quantity of fetal hemoglobin (HbF) which consists of 2 alpha and 2 gamma globin chains is one possible therapeutic approach. Gamma globin is normally suppressed after birth such that HbF is less than 1% of the total normal adult hemoglobin. However, 5-azacytidine, hydroxyurea, and cytosine arabinoside, toxic chemotherapeutic agents, can increase HbF synthesis. These drugs may arrest the growth and maturation of erythroid progenitors that have repressed gamma globin gene expression. Responses of patients to these drugs have been variable and large studies will be necessary to determine their role in the treatment of HbSS.

The red cell internal environment and membrane have been the targets of investigations, the results of which may lead to effective stroke prevention and treatment. The physiologic principle underlying several therapeutic approaches is that reduction of the mean corpuscular hemoglobin concentration (MCHC) will reduce HbS polymerization. Hyponatremia results in swelling of the red cell and consequent lowering of MCHC, and hyponatremia induced by the administration of hypotonic fluids, low salt diet, diuretics, and synthetic long acting vasopressin results in serum sodium concentrations of 120 to 125 millimoles per liter, decreased MCHC, and reduced red cell sickling. Chronic therapy has been associated with fewer crises and acute therapy with shorter crises, but for central nervous system diseases including stroke, the consequences of hyponatremia such as seizures and brain swelling require very careful evaluation before this therapy can be routinely adopted.

Perhaps the most promising development in the treatment of HbSS is the discovery of agents acting on the erythrocyte membrane such as cetiedil and pentoxifylline. Cetiedil has no direct effect on HbS but does prevent sickling and increases red cell filterability presumably by a direct effect on the red cell membrane where labeled cetiedil can be located. The drug pro-
motes a net gain of intracellular sodium and water resulting in cellular swelling and reduction of MCHC. Whether this cellular swelling will prevent the hoped for increase in microcirculatory flow expected with reduced sickling remains to be seen. Pentoxifylline’s effect is by increasing the deformability of the red cell and the drug has been shown to improve perfusion in the microcirculation. Peripheral vascular resistance and viscosity are lowered in HbSS after treatment with pentoxifylline although the drug has no effect on hemoglobin binding to oxygen or the solubility of deoxy-HbS. Two patients with HbSS have noted decreased number of crises with pentoxifylline treatment.

Paroxysmal Nocturnal Hemoglobinuria

This unusual red blood cell disease is due to an acquired disorder of the hemopoietic stem cell resulting in an increased susceptibility of the mature erythrocyte to lysis by complement. This results in intravascular hemolysis and hemoglobinuria worse during respiratory acidosis occurring with sleep. Leukopenia and thrombocytopenia often occur, and strokes result from cerebral venous thrombosis triggered by liberation of thromboplastin from hemolysed red blood cells and hyperaggregable platelets. One reported case has been linked to the onset of estrogen therapy, and cerebral vein thrombosis has been associated with pregnancy in several reports.

Cases are too few for a concensus on therapy, but for acute venous thrombosis heparin and/or warfarin should be considered keeping in mind the hemorrhagic propensity of strokes due to venous occlusion. When extensive hemolysis occurs, high dose steroids may be effective and transfusion may suppress the production of complement sensitive cells.

Chronic therapy with androgenic steroids may stimulate red cell production, and corticosteroids (prednisone 15-40 mg qd at bed time) have also been reported to prevent red cell lysis though the mechanism is unclear. Most patients are severely iron depleted, but iron therapy must be approached cautiously due to the burst of erythropoiesis and subsequent hemolysis stimulated by iron replacement. Transfusion therapy may be necessary but may aggravate hemolysis by introducing a substance from the donor’s plasma which activates the patient’s complement.

Polycythemia Vera And Secondary Polycythemia

Polycythemia vera (PV) is a myeloproliferative disease arising from a fundamental stem cell disorder in which there is inappropriate overproduction of erythroid, myeloid, and megakaryocytic cell lines in the bone marrow (panmyelosis). Typically this disorder is insidious in onset occurring in middle-aged or elderly patients, and may be an incidental finding on blood work drawn for an unrelated reason. Patients with more advanced peripheral blood abnormalities may present with symptoms related to impaired circulation to the heart, peripheral vascular, or central nervous system. Typically the red blood cell count ranges from 6,000,000 to 9,000,000/mm³ with normal indices unless iron deficiency is also present which is not uncommon. There is generally a moderate granulocytosis less than 20,000/mm³ but much higher counts in the range of chronic myelogenous leukemia (50,000–100,000/mm³) can be seen. Platelet counts can also be elevated in the range of 500,000 to 2,500,000/mm³ particularly if there is accompanying iron deficiency, infection or other inflammatory process. The bone marrow is grossly hypercellular with increased marrow reticulin fibers. After a variable number of years the disease may progress through a “spent phase” which in its blood and marrow manifestations resembles myelofibrosis and agnogenic myeloid metaplasia with anemia or other cytopenias, hepatosplenomegaly, and marrow fibrosis.

Secondary polycythemia may occur in the context of a physiologically appropriate increased erythropoietin production in response to hypoxia. The cause of tissue hypoxia could be high altitude, severe chronic obstructive pulmonary disease, cyanotic congenital heart disease, hypoventilation of massive obesity (Pickwickian syndrome), or red cell disorders such as high oxygen affinity hemoglobinopathy. Erythropoietin may be non-physiologically increased in association with kidney abnormalities such as cysts and hydronephrosis, or in association with certain neoplasms (hepatoma, renal or ovarian carcinomas, fibroid tumors of the uterus, adrenal adenomas, or cerebellar hemangioblastoma). Elevations of hematocrit can also be unassociated with increased erythropoietin and red cell mass which is the syndrome of “stress” polycythemia (Gaisbock’s syndrome).

Polycythemia of whatever type causes cerebrovascular symptoms not by causing arterial or venous obstruction, but because of heightened whole blood viscosity resulting from increased red cell mass. The heightened viscosity is associated with reduced CBF resulting in symptoms of global cerebral dysfunction such as mental slowness, lethargy, dizziness, tinnitus, and headaches. The inverse relationship between Hct and CBF is seen even in normal ranges of Hct from 36 to 53%, and lowering Hct by isovolemic phlebotomy results in increased CBF and amelioration of symptoms.

The physiologic basis for this CBF-Hct paradigm is debated since it is unclear whether Hct associated CBF changes are a direct consequence of changes in viscosity, or a response to altered oxygen carrying capacity.

Several studies have associated high Hct and viscosity with increased stroke risk and morbidity from stroke. While polycythemia rarely if ever plays a causal role in focal cerebral infarction, it is likely that a high hematocrit impedes reperfusion in the microcirculation and that cautious lowering of Hct is a reasonable therapeutic approach in patients with acute cerebral ischemia and high hematocrit.

Anemia

As with polycythemia, anemia usually causes global rather than focal cerebral ischemic symptoms. Sickle
et al, however, published a remarkable report of 5 normotensive patients with severe anemia (hemoglobin <10 grams per 100 cc) due to chronic blood loss who presented with focal cerebral ischemia symptoms. In all cases, symptoms disappeared with transfusion, and the anemia was felt to have unmasked previously asymptomatic occlusive lesions and borderline oxygen delivery in the carotid or vertebralbasilar circulation.  

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**Diaschisis**

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A BETTER UNDERSTANDING of the mechanisms of spontaneous recovery following stroke may provide insight into achieving clinical investigative measures to accelerate and enhance post-stroke recovery. This progress review focuses on one such mechanism, Von Monakow’s controversial and often misunderstood theory of diaschisis. Although the extensive literature on recovery of stroke function is not reviewed, selected studies and theoretical issues potentially related to diaschisis are discussed.

Diaschisis is but one of several general theories of recovery of function which classically include: a) vicariation—the taking over of functions of the damaged area by regions not originally involved in the performance of lost behavior, b) redundancy—recovery based upon uninjured neurons that normally contribute to the function, c) compensation—the taking over of functions of damaged areas by intact regions remote from but connected to the area of damage.
Red blood cell disorders and stroke.
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