EDITORIAL

Sickle Cell Disease

THE BELATED RECOGNITION of the importance of sickling as a cause of sickness and death in young black people in this country has led to an energetic mobilization of resources to combat sickle cell disease. The prospect of increased funds from government and private sources for the investigation of sickling has understandably heightened the level of interest and activity in many relevant areas. The fact that the biochemical abnormality and its pathological consequences are so much better delineated in sickling than in most other serious diseases has led to the notion that the most notable deficit in our care of sicklers is in the delayed application of our knowledge to the treatment of patients with sickle cell disease and to the detection of individuals with sickle cell trait. In part, these ideas stem from the previous lack of support for descriptive clinical investigation in sickle cell disease; it is shocking that we cannot better define the causes of death in this common disorder. We cannot even state with certainty the incidence of splenic sequestration crises in children or the most frequent circumstances associated with fatal vasoocclusive crises in any age group. The indications for blood transfusion in sickling have never been defined and seem to depend on such vagaries as the previous experience of the consulting hematologist. The need for programs of sound clinical observations and investigations is clear, and improvement in patient care will reflect the superior professional care generally accorded to patients whose disorders are being actively investigated. The hard reality remains, however, that no specific treatment for vasoocclusive crises, or for the chronic anemia, or for the organ damage that is probably consequent upon infarctions and anemia is yet available for patients with sickle cell disease, although several agents are now being evaluated. Nalbandian found that the intravenous infusion of urea in invert sugar led to dramatic improvement in the symptoms of sickle cell crisis, and he and others have shown that urea in relatively high concentrations will impair the sickling of red cells containing hemoglobin S. Nalbandian’s protocol requires administration of the urea-invert sugar solution through a central venous catheter and careful monitoring of levels of blood urea as well as of the extent and character of the urea-induced diuresis. It is difficult to know how many patients with sickle cell crises are treated in hospitals in which the professional and laboratory demands of such a protocol could be met only with considerable effort, particularly in times outside the usual working day. While Nalbandian indicates that intravenous urea is without hazard if his regimen is followed precisely, the possibility exists that, in a busy intensive care unit, details of the protocol may occasionally be inadvertently overlooked and that therapeutic misadventures will occur. Some of the patients with frequently recurring crises of a mild nature might understandably prefer analgesics and oral or parenteral hydration to the more complicated experimental treatment with intravenous urea.

Nalbandian began his studies of urea as a therapy for sickle crisis on the
hypothesis that urea would interfere with the intermolecular hydrophobic bonds of deoxygenated hemoglobin S, postulated by Murayama as the molecular basis of sickling. Neither the sites nor the types of intermolecular bonds in unliganded sickle hemoglobin have been conclusively demonstrated, and the concentrations of urea achieved in the red cell in vivo would be unlikely to interfere with hydrophobic bonds.

The premature publicity given to urea as a treatment for sickle cell disease in the daily press before evaluation of its efficacy had been published in medical journals aroused considerable confusion and hostility about the use of urea. However, other investigators, notably McCurdy and Mahmood, have also observed some apparently beneficial effects of urea in sickle crises (also in uncontrolled studies), and Bensinger et al. who demonstrated significant increases in carbon monoxide production following the administration of urea to sicklers have suggested that urea therapy might lead to early lysis of cells most susceptible to sickling. The need for further studies is obvious, and urea remains an experimental agent for the treatment of sickle cell crisis.

The publicity accorded to urea has had certain incidental beneficial effects: (1) it emphasized the inadequacy of our knowledge about the pathogenesis and treatment of sickle cell crisis, and (2) it has sharpened our awareness of the necessity for carefully designed clinical trials of pharmacologic agents for sickling. The latter statement may appear simple-minded in an era of logarithmic growth of clinical pharmacology, but, even in the recent past, objective evaluations of a number of agents said to ameliorate sickle crises have been minimal. In a disorder as variable in its onset, intensity, and duration as sickle cell crisis, objective appraisal of the effects of the treatment of large numbers of affected patients and of patient-controls is necessary to establish the role of urea or of any form of treatment. Such studies of urea therapy are now being done by several investigators with support from the National Institutes of Health, and unequivocal data concerning the usefulness of intravenous urea in sickle cell crisis should be soon available. In view of the number of individuals affected and the severity of the symptoms, it would seem appropriate for definitive data concerning the therapeutic effects of intravenous urea in sickling to be released to the medical profession as promptly as possible.

Another promising lead in the potential therapy of sickle cell disease is being developed by Cerami et al. at Rockefeller University. They suggested that the benefit attributed to urea might actually be related to cyanate which is in equilibrium in solution with urea. They found that cyanate, which reacts with N-terminal residues to yield carbamylated proteins, impaired sickling of red cells in which the sickle hemoglobin had been carbamylated. Both urea and cyanate impaired sickling in vitro, but the necessary concentration of cyanate was considerably smaller. However, two lines of evidence suggest that the presence of cyanate does not account for the inhibition of sickling by solutions of urea: (1) the impairment of sickling by urea is no longer demonstrable after the removal of urea from the erythrocytes by washing, although sickling is still impaired in cyanate-treated erythrocytes following removal of the cyanate; (2) while the carbamylation of hemoglobin by cyanate requires time, sickling is impaired promptly when erythrocytes are exposed to solu-
tions of urea. Treatment of the red blood cells of sickle cell anemia patients with cyanate leads to prolonged in vivo red cell survival. There appears to be no evidence for the conversion of cyanate to cyanide; the principal theoretical reservation about the administration of cyanate to human subjects is the potential carbamylation of other intracellular or extracellular proteins. Cerami et al. are carrying out a number of careful studies designed to ascertain the immediate and long-term toxicity and usefulness of cyanate. Until some of these studies have been completed, cyanate must be considered a promising, but still experimental form of therapy for sickle cell anemia.

Kraus et al. have found that carbamylation of hemoglobin can also be achieved by the exposure of erythrocytes to carbamyl phosphate. The role of this compound in the therapy of sickle cell disease also remains to be determined.

While the reports of urea and cyanate have excited a good deal of interest, other forms of therapy for sickle cell disease and for some of its complications also merit investigation. The efficacy of alkalinization and the role of transfusions in the management of sickle cell disease should be examined critically. In some clinics, patients with sickle cell anemia receive routine prophylactic antibiotics, while in other clinics antibiotics are given only for demonstrated infectious disease. Folic acid is administered routinely in some clinics to sicklers and is rarely given in others.

It would be highly desirable for a number of clinics to cooperate in well-designed studies of the natural history and treatment of the less common complications of sickling; the "chest syndrome" in which pleurisy, fever, and infiltrates demonstrable by X ray are variously attributed to pneumonia, embolism, or thrombosis in situ with infarction must be susceptible to better definition in hospitals with modern techniques for pulmonary visualization. How should the central nervous system manifestations, ranging from mild peripheral weakness to acute subarachnoid bleeding, be managed? What are the indications for surgical intervention in aseptic necrosis of the femoral head? Some patients in whom X rays reveal severe deformity of the hip joint have little chronic functional impairment. The recent report of alarmingly high maternal mortality and fetal wastage in sickle cell anemia strongly suggests the need for objective examination of obstetrical experience in other centers and evaluation of the indications for abortion, as well as for the use of transfusions and other supportive measures, in pregnant sicklers. The pathogenesis and management of the serious "sequestration crisis" of young children, of priapism, of the all too common leg ulcers, of hematuria, and of the ocular sea fan hemorrhages and vitreous bleeding of sickle cell hemoglobin C disease could surely be better defined with data from carefully planned and conducted cooperative studies.

It is clearly unwise to decide that research in sickling should now exclude basic biochemical and biophysical research programs. Sickling accompanies the gel formation that occurs when hemoglobins containing valine instead of the normal glutamic acid as sixth residue of the \( \beta \)-polypeptide chain are deoxygenated, but the molecular organization of the resulting tactoid or gel remains unclear. Deoxyhemoglobin F is apparently excluded, but other hemo-
globins participate in the sickle gel. In mixtures with hemoglobin S, certain hemoglobins, e.g., those containing substitutions at B6 or B121, appear to favor polymerization and gelling,9,10 while the substitution of asparagine for aspartic acid at B71 appears to impair gelling.11 The recent findings of Bookchin and Nagel12 that the deoxy conformation is necessary for hemoglobin S but not for hemoglobin A, which interacts equally well in deoxy or the cyanmet form (oxy conformation), suggest that the site complementary to the B6Val determined binding site in the gel is equally exposed in the oxy or deoxy conformation. They suggested that the tactoids of sickle cell hemoglobin represent a helical structure of low pitch with at least two binding sites, and, from the electron microscope studies of White13 and of others,14,15 such a helical structure would have about six molecules per turn. Clearly, much better definition of the nature of the sickle tactoid will emerge from continuing studies utilizing electron microscopy and from further observations on interactions of hemoglobin S with hemoglobin variants or chemically modified hemoglobins.

An important role of the red cell membrane in the sickling of the erythrocyte has been suggested by the studies of Bertles and Milner16 on irreversibly sickled cells, and by the observations of Jensen17 on the fragmentation of sickle cells in the sickle-unsickle cycle. From electron microscopy studies, White has also suggested important interactions of red cell membranes in sickled erythrocytes.13 However, the role of the red cell membranes in sickling is virtually unexplored at the biochemical and biophysical levels.

Modification of the clinical and laboratory manifestations of sickling by other variables in the red blood cell deserves further exploration. The concomitant presence of electrophoretically “silent” hemoglobins, of mild thalassemia or of variants of glycolytic enzymes might serve to explain some of the great differences in clinical severity of sickle cell disease. That we know the primary genetic defect in sicklers should not suppress efforts to find genetic or environmental explanations for its variable clinical expression.

Programs devoted to screening of individuals for the presence of sickling, which are being instituted in many urban centers, have generated numerous questions: who should be screened?; when should screening be done?; how should the results of the screening tests be handled?; should screening be voluntary or mandatory?; what methods should be used for screening?; and even, should screening be done at all? Clearly if sickle cell trait affects one in 10 or 12 black Americans and sickle cell disease one in 400, the vast majority of individuals detected by a screening program will have sickle cell trait. The institution of any screening program should begin with the education of community workers, lay or professional, who will have the principal responsibility of explaining the benign nature of sickle cell trait to parents or to individuals in whom sickle cell trait has been established. At the same time, vigorous efforts to educate both the lay and medical communities about sickle cell trait and sickle cell disease must be made. A child who is found to have sickle cell trait is hardly benefited if he is then treated as “different,” or if this information is utilized to deny him employment or life insurance in the future. Because sickle cell trait is rarely associated with hematuria, or with splenic infarction
at low oxygen tensions, or, and, here the evidence is less clear, with complications of anesthesia, physicians have occasionally mistakenly attributed other symptoms to sickle cell trait. That appendicitis in an individual with sickle cell trait has been observed as an abdominal crisis indicates the need for professional education about sickling. The wisdom of the founders of one of the large organizations devoted to sickling is to be found in its title: The Foundation for Research and Education in Sickle Cell Disease. The educational component has been regarded as an arm of a screening program; it would better be considered as its heart, for without well-trained community workers for this specific educational mission, there is serious doubt as to the viability or the desirability of mass screening for sickling. No such definitive recommendations can be offered for other questions about screening programs. Certain states have instituted screening programs that are nearly mandatory for school children, although many of us would have preferred to see smaller voluntary pilot programs during which screening methodology could be evaluated and community-worker training programs developed.

Five groups have been mentioned in the design of the screening programs of black and Latin population groups: (1) pregnant women, (2) newborns, by cord blood screening, (3) school children, at the time of entering school or during adolescence, (4) military recruits, and (5) premarital screening. Sickling tests on pregnant women could be classified not as screening, but rather as laboratory tests appropriate to medical care, in view of the probable administration of anesthesia and the evidence for increased incidence of urinary tract infections in sickle cell trait during pregnancy. Screening of cord bloods is in reality a case-finding method for sickle cell disease; with agar gel electrophoresis at pH 6.0 sickle cell anemia can generally be distinguished at birth despite the presence of large proportions of hemoglobin F. The recognition of sickle cell anemia at birth has many advantages; genetic counseling of parents can be done before another pregnancy, and the prompt diagnosis of sequestration crisis and of dactylitis which occur in young children is facilitated.

The screening of black and Latin school children would optimally include other tests; glucose-6-phosphate dehydrogenase deficiency with its susceptibility to anemia during infections or after exposure to drugs is as common as sickle cell trait, and nutritional deficiencies are frequent in groups being examined for sickling. In most groups screening programs in which the presence of hemoglobin variants, of G-6-PD activity, and of anemia were evaluated would be considerably more valuable than simple screening for sickling.

If the results of sickle screening are to be utilized for genetic counseling, i.e., the explanation of the formal genetics of sickle cell disease in order that the individual who has sickle cell trait may make informed choices in marriage and in procreation, two conclusions are obvious. (1) The screening should be done during adolescence when the individual can better understand the genetic aspects of sickling, and (2) the screening methods utilized should include a solubility test (for hemoglobin S) and an electrophoretic pattern to detect interacting hemoglobins, particularly hemoglobin C, and perhaps β-thalassemia trait. The combination of a macroscopic solubility test which
can be automated, together with recently developed simplified electrophoretic methods which do not require the preparation of hemolysates, appear to be significant advances in large-scale screening techniques.

There are obvious problems for the individual concerned if screening is carried out at the time of the premarital examinations. Genetic counseling could be done, but the psychological problems engendered by premarital screening may make it undesirable at least at the present time. Screening of military recruits would appear to be desirable from many aspects; reports of splenic infarction at low oxygen tensions and of death on sustained strenuous exercise in individuals with sickle cell trait should be considered in military assignments. In addition, recruits with previously undetected mild sickle cell anemia or sickle-cell hemoglobin C disease can be recognized prior to actual military service.

In many parts of the country, present clinical facilities are probably sufficient for the medical care of patients with sickle cell disease (as opposed to trait) who are first discovered during screening programs. Many of these patients have infrequent acute illnesses, and others may be already receiving medical care for joint pains or anemia. The principal additional facilities for medical care which may be required in some communities will be for office or outpatient visits. The requirements for optimal patient service suggest that some mechanism be established for the more detailed evaluation of unusual laboratory findings noted in screening programs. Perhaps a laboratory in a large hospital in a given geographic area should be designated as a regional laboratory with dual responsibilities of maintaining quality control in the laboratory aspects of the screening programs and of evaluating unusual blood samples in greater detail.

This is an exciting time for those interested in sickling. Recent advances in many relevant fields offer the prospect of a new era in the management of this common and disabling disease.

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