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In this issue of *Public Health Reports* appear three articles relevant to understanding the treatment needs, hospital utilization patterns, and medical costs of sickle cell disease patients in the United States. Taken together the papers remind us of the terrible health burden imposed on individuals and society by this genetic disease. However, the papers also indicate the existence of great variability in the need for medical treatment among sickle cell patients and in the availability of that treatment in different localities. These variabilities must be understood if we are to optimize therapy for this disease, which is prevalent among African-Americans and certain Hispanic groups in this country.

Sickle Cell Disease Expenditures and Outcomes

The first paper, by Davis et al., uses data for 1989 through 1993 from the National Hospital Discharge Survey to estimate that there are about 75,000 hospitalizations per year in the United States of patients with sickle cell disease, with an estimated average cost (in 1996 dollars) of $6300 for each hospitalization. Thus, these illnesses add about half a billion dollars annually to overall U.S. hospitalization costs, most of which is borne by various government programs.

The paper by Woods and colleagues fills in details of this national picture with an analysis of hospital utilization by sickle cell patients in Illinois during the calendar years 1992 and 1993. The most striking results of this study are that more than 97% of the admissions were for painful crisis and that 4% of the patients accounted for almost 25% of hospital admissions. The median number of admissions per patient was three but ranged from one to 116! The authors encourage the development of targeted programs for adult sickle cell patients, especially for the small subgroup of high risk patients.

The third paper, also by Davis and his colleagues, contains both good and bad news for the public health and medical communities. The authors used 1968 to 1992 U.S. death certificate data to calculate mortality rates of 1- to 4-year-olds by geographic region. Very encouragingly, this rate for the United States as a whole fell from 10.5 per thousand person-years in the 1968–1980 period to 6.8 in the 1981–1992 period. Disturbingly, however, there were very large variations in the death rate from state to state and in comparisons of various counties and cities within each state in both the early and recent periods. The authors suggest that access to and quality of care in each region of high mortality should be evaluated.

What lessons should the public health and biomedical research communities draw from these three papers? First, we note that although nationwide hospitalization costs are substantial—at about a half billion dollars per year—it is likely that these calculations are a marked underestimate. Extensive emergency room and non-hospitalization-based treatment, as well as other social costs, must also be considered, making the actual financial burden to society much greater.

However, an immediate consequence of these current hospitalization expense data is to put the costs of newly developing therapies for sickle cell disease—such as hydroxyurea to elevate fetal hemoglobin[1] or bone marrow transplantation from histocompatible antigen-identical siblings[2]—into perspective. The pharmaceutical and medical charges for a year of hydroxyurea treatment, including the necessary frequent clinic visits and laboratory tests, has been estimated at approximately $3000 (Samuel A. Charache, MD; personal communication), and the treatment is expected to reduce crisis frequency on average by about 50%. The cost of a typical bone marrow transplant procedure has been estimated at $100,000 to $200,000 by Mark Walters, MD, the lead author of the recent *New England Journal of Medicine* article on bone marrow transplantation.[2] It is very clear that costs of conventional therapy for the small group of sickle cell patients who need frequent hospitalizations are in the long run much greater than the ongoing costs of hydroxyurea therapy or the high initial costs of transplantation. It must be recognized by health insurance companies as well as by public health authorities that perceived financial barriers should not be allowed to impede the development and availability of these new therapies if they are proven efficacious and safe. Continued research into other agents to increase fetal hemoglobin and into optimizing bone marrow transplantation would be well justified on financial as well as humanitarian and scientific bases.

Second, the falling mortality rates since the 1968–

1980 period strongly suggest that conventional supportive therapies do make great differences for patients. These benefits had been inferred from old controversies about possible differences in the general severity of sickle cell disease between sub-Saharan Africa and the United States or between the United States and Jamaica.[3] We now understand that most of these controversies were due to differences in availability of health care and to other factors, such as nutrition and immunizations, related to standards of living. Conversely, the use of health statistics to identify regional variations in death rates and other health parameters is potentially a powerful tool for use by government authorities to improve public health and potentially identify other risk factors. As regions with marked differences from the mean are identified, one would expect manifold pressures to identify the causes of these situations and to rectify them. Further, with time we should expect to see not only continued lowering of mean values of death rates but also a narrowing of the variances in rates as medical expertise increases and diffuses throughout the nation.[4]

Lastly, what can the biomedical research community learn from these new data? It would seem to me that one conclusion from these studies is the continued need to understand the paradoxical heterogeneity of this apparently simple genetic disease.[5] Some sickle cell disease patients have no painful crises; others have dozens each year. Some die in the first few years of life; many live virtually normal life spans.[6] Although sickle syndromes can be caused by the presence of one sickle (S) gene in conjunction with a beta-thalassemia or a hemoglobin C gene, the vast majority of sickle cell patients are genetically uncomplicated in that they are homozygous for two S genes. Why then the extraordinary variation in clinical manifestations? Although co-existing alpha-thalassemia and variations in the levels of fetal hemoglobin account for some of this clinical variability, most is unexplained despite decades of intense research on the attributes of the sickle erythrocytes and blood of these patients.[7] Perhaps very recent exciting work on new aspects of the control of oxygen delivery and vascular tone by nitric oxide[8] and other physiological modifiers will shed light on this paradox. Such physiological studies also hold the potential of opening up largely unexplored therapeutic approaches.

It is clear that continued research is needed on the pathophysiology and treatment of sickle cell anemia at the genetic, protein, cellular, physiological, and clinical levels. The investment of public research dollars in this disease in the half century since the 1945 discussion of Linus Pauling and William B. Castle that led to the concept of a molecular disease[9] has paid off many fold, both for the treatment of patients with sickle cell anemia and for new biomedical concepts that have illuminated many other disease processes.

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