Sickle Cell Anemia: National Program Raises Problems as Well as Hopes

Two years ago, sickle cell anemia was a relatively obscure disease. Black children with sickled blood, and their families, knew and cared about it. So did a comparatively small corps of physicians and researchers. Even though this disorder is one of the more prevalent of inherited diseases—it occurs, for example, in 1 in 500 live births, compared to cystic fibrosis, which occurs in 1 in 1400 live births—because it almost exclusively afflicts black people, sickle cell anemia had remained in the background, out of sight.

It suddenly entered the national consciousness when the President called for a special effort to combat the disease in his 1971 health message. Through a series of essentially political events, sickle cell anemia achieved national prominence. Last spring, Congress passed the National Sickle Cell Anemia Control Act. Plans to expand research and to launch an extensive campaign to screen black persons for sickle cell trait were put into operation.

In an earlier article (*Science*, 13 October 1972), some of the events that led to the passage of that legislation were discussed, and some of the difficult problems it has raised were mentioned. For instance, some persons who carry sickle cell trait, which many experts believe to be a benign condition, allegedly are having trouble obtaining life and health insurance and are being discriminated against on the job. The prospect of mass screening of black children and young adults for sickle cell trait raises other thorny problems.

First, there is the technical matter of the screening test itself. According to Robert Murray of Howard University in Washington, D.C., there are several tests around, but three predominate. One is a solubility test, in which a drop of blood is mixed in solution. If the solution turns cloudy, one presumes the presence of an abnormal hemoglobin, which may or may not be sickle hemoglobin. Follow-up tests are required to pin down the nature of the disorder if the solubility test is positive. Sickledex is one of the commonly used brand-name versions of this test and costs about 2 cents per test for materials. It can be conducted by virtually any technician.

Another method of screening for the trait involves observing blood cells under a microscope to determine whether sickle hemoglobin is present. But, because that test requires equipment most community screening programs lack, it is not widely used.

A third technique, one preferred by a number of investigators, is hemoglobin electrophoresis—a method of distinguishing molecules on the basis of their electrical charge. Says Howard Pearson, a pediatric hematologist at Yale University School of Medicine, "Sickledex is nondefinitive and of historical interest only. It comes up with wrong answers and is scaring people half to death. Hemoglobin electrophoresis is the only test you can defend." According to Pearson, whose laboratory is active in this field, electrophoresis costs about 5 cents per test for materials. A technician can run 100 to 150 a day. Pearson concedes that he is "very prejudiced in favor of electrophoresis, because it is definitive and picks up sickle cell anemia, sickle cell trait, and other hemoglobin disorders such as C-trait, a related condition of abnormal hemoglobin."

Another thing to be said for electrophoresis, investigators now maintain, is the very fact that it is just slightly more complicated to perform than the solubility test. Therefore, programs using electrophoresis will probably be affiliated with a medical center or hospital that can provide backup support and counseling to persons whose tests are positive.

Experience to date with mass screening for sickle cell disorders has made it apparent that issues pertaining to education, the law, community relations, and the private lives of individuals are in urgent need of resolution. Roland Scott, a black physician at Howard who has been studying sickle cell anemia for 25 years, is profoundly disturbed about what he sees as a lack of education and counseling in many screening programs. "Education," he declares, "has been sorely neglected in the rush to run out to stick somebody and take his blood. Well, it's just not as simple as that." Murray, Pearson, and others who have been involved in sickle cell programs adamantly agree.

At issue, they believe, is not merely identifying carriers of sickle cell trait, but helping those individuals and society at large understand what being a trait carrier means. A person's reaction to being told that he carries sickle cell trait and could, therefore, have a child with sickle cell anemia if he marries a trait carrier, apparently depends in part on how much he knows about the condition *before* he is screened.

"We try to explain to the couples we have counseled that not all of their children will necessarily have the disease and that, in many respects, even people with the disease can lead productive lives. It is not as horrible as it is sometimes made out to be," says Murray. "We emphasize the fact that couples must make their own decision about children and not rely on other people's experience. Sometimes we have to allay fears that having a sickle cell child means God is angry. We tell them that God doesn't punish people through their children, that in many ways our genes are an accident of nature. Usually, couples come to us scared and leave somewhat relieved."

Trait Carries Stigma

Murray is not trying to minimize the horrors of sickle cell anemia, the pain that accompanies a sickle cell crisis (during which tissues are starved of oxygen because the sickled cells have jammed the small vessels in the body), the frequent bouts of illness that plague the lives of children with sickle cell anemia. But he, like many of his colleagues, believes that the disease needs to be better understood, to be put in perspective. Similarly, people need to be taught that being a sickle cell trait carrier is not a cause for shame. "There is a real stigma attached to carrying the trait," he observes. "The trait is a mutation, and that is thought to be a bad thing by our society. And some people confuse genes with germs and think they're carrying something dangerous."

Given this kind of ill-founded, but nonetheless real, reaction of carriers of

sickle cell trait, investigators are trying to cope with the question of when, or even whether, to screen large groups of black people. Here, in many instances, they are going to have to deal with state legislatures.

In an enthusiastic reaction to the national effort to combat sickle cell anemia, states have rushed into law provisions for screening for sickle cell trait. Some are voluntary; some are not. On this point, most physicians are in accord. Screening programs, they insist, should be voluntary. But even if they are voluntary—at least on the face of it—problems arise over the question of when to screen.

Connecticut, where radio and television stations (WTIC) owned by Leonard J. Patricelli, have conducted a powerful sickle cell campaign beginning as early as November 1970, was the first state to pass legislation for screening for trait carriers. The law said screening was to be voluntary. The experience in the state has been mixed.

In Hartford, where WTIC is based, efforts were made to screen all black children in grades 7 through 12. Three weeks before the proposed week for screening, permission slips were sent to 5000 parents. The news media frequently referred to the upcoming test week on both radio and television, as well as in the papers. A total of 3456 children were screened by the Sickledex method; 301 tests were positive, and follow-up studies by hemoglobin electrophoresis showed that four children did not carry the trait after all. No one was notified of the test results until after the follow-up electrophoresis had been done.

The Hartford study was conducted with a large measure of community cooperation, which seems to be why so many students and their parents responded. The project has been criticized, however, for screening children as early as the seventh grade. These children, it is argued, are too young to fully understand the implications of being a trait carrier, could suffer from the stigma, and may forget all about it by the time they are likely to be considering marriage and child-bearing. "Testing young school kids is crazy," Pearson says flatly. Others contend that the screening has done no damage to anybody. Some studies are under way to sort out these various points of view, but they are not likely to come up with much solid data for quite a while.

Some other screening projects in Connecticut have not been as successful at attracting people to be tested. In New Haven, for example, community response was very low. The problem, Pearson believes, was that a conflict developed between black medical students at Yale, who were organizing the project, and local black leaders. "People apparently felt that screening was being forced on them, and they wouldn't go along with it," he explains.

The feeling that a "voluntary" screening program was not voluntary at all apparently caused the downfall of a project that was being set up for employees at the National Institutes of Health (NIH) in Bethesda, Maryland, not long ago. According to white NIH officials, the program was "ill conceived, to say the least." In that situation, black employees resented the fact that they had not been drawn into the planning of the program, feared that if they were discovered to be trait carriers it would be included in their medical records and could jeopardize their jobs, and felt that they were going to be experimented on in a way they did not like.

Similar situations apparently have existed elsewhere. They point up the complexities of screening and, some medical and community leaders contend, raise the question of whether we should engage in mass screening for sickle cell trait at all.

Eugenic Implications Skirted

In essence, some persons are saying that it is not really clear what these screening programs are all about. "The problem," said one NIH official, "is that no one is facing up to the eugenic implications of informing someone he carries sickle cell trait."

Generally, physicians who have been involved in sickle cell research concur that, if you can inform an individual that he carries the trait, you should. Just what he is supposed to do with that information is less clear. The only way he can be sure not to have a child with sickle cell anemia is either to avoid marriage to someone who also carries the trait or to forego having children. Yet those responsible for counseling these people insist that they are not telling them to make one of those choices; they are telling them the decision is theirs. "That sort of thing sounds fine, but really is a bit abstract," says one investigator who is beginning to doubt the assumption that the knowledge of being a trait carrier is *necessarily* good. "Perhaps we should wait until we have more to offer these people before we go around handing out such information so casually," he says.

The issue is not likely to be resolved soon. One choice that some investigators feel trait carriers should be offered is in utero diagnosis. With Tay-Sachs disease, a fatal genetic disorder that primarily strikes Jews of northern European ancestry, for example, it is possible to monitor the pregnancy of a couple who have been found through screening to be at risk. Doctors can tell whether the fetus does or does not have this disease in time to perform an abortion if the couple wishes it. No similar test yet exists for sickle cell anemia, but theoretically one could be perfected.

A team from the Johns Hopkins University, which included Michael Kaback, Morley Hollenberg, and Haig H. Kazazian, first reported a year ago (*Science*, 12 November 1971) that it is possible to detect sickle hemoglobin in a fetus. The problem is that, in order to perform the test, one needs a drop of fetal blood. Amniocentesis, as it is carried out now, is a procedure in which amniotic fluid is withdrawn and examined for evidence of disease in the unborn child. Drawing blood from the fetus itself, however, poses an additional difficulty. It will be necessary to take blood from the heel, Kaback has said, and, in order to do that, one has to be able to *see* the fetus. Techniques for this have yet to be developed.

Investigators in Boston have also reported similar success in identifying sickle hemoglobin in the fetus (the fetuses that were studied were obtained at abortions that were performed for medical reasons), and work in this area is continuing, although not in an extensive way. According to Rudolph Jackson, head of the national sickle cell anemia program, which is being coordinated through the National Heart and Lung Institute (NHLI), none of the $9 million allocated for the program for fiscal year 1972 is being spent on in utero diagnosis. The reason he gives is that this area of research is too sensitive, raises too many thoughts of genocide. "We're just not ready to support this yet," he told *Science*.

The $9 million in Jackson's hands has been divided almost equally between screening and education programs and programs in research, a division that was made under the direction of a special sickle cell disease advisory committee. At the present time, there is no cure for sickle cell anemia. Many of its victims die before they are 20 years old. Few live beyond

40. Existing forms of therapy leave much to be desired.

During the last couple of years, two new therapeutic agents have been proposed and have attracted considerable attention in the medical community and in the press. One is urea; the other, cyanate. Each attacks the problem of sickle cell anemia where it counts—at the molecular level, by reversing sickling, at least in vitro. Each comes from an understanding of the molecular basis of the disease. Whether either actually works in patients is very much open to question. Many investigators say it is not at all clear that these agents will reverse sickling at dosages that are safe in human beings.

Sickle cell anemia is among the first diseases to be dissected at the molecular level. Initial inroads into an understanding of sickle cell anemia were made by Linus Pauling and his colleagues, who first showed in 1949 that normal adult hemoglobin and sickle hemoglobin are structurally different molecules (*Science*, 25 November 1949). In a paper titled "Sickle cell anemia, a molecular disease," Pauling correctly suggested that sickle cell hemoglobin molecules are capable of interacting with one another, that upon deoxygenation, the molecules can aggregate into rods that twist fragile red cells out of shape.

By 1957, V. M. Ingram, now of the Massachusetts Institute of Technology, had taken molecular studies of the sickle cell further. He demonstrated that, structurally, sickle cells differ from normal ones at only two positions in a molecule that is made up of 574 amino acid residues. Following up on this information, a physical chemist at the National Institutes of Health who had once studied under Pauling explained how the substitution of valine for glutamic acid in the two positions affects the cell in such a way as to allow sickling. Makio Murayama, who has made a precision model of sickle cell hemoglobin, published the "Molecular mechanism of red cell sickling" 6 years ago (*Science*, 8 July 1966).

Working with Murayama's molecular explanation, a Michigan physician set about finding a chemical that would break the bonds which form to distort hemoglobin into a sickle shape and came up with the observation that urea, commonly used in chemical and medical experiments, appears to do so. This observation by Robert M. Nalbandian of Blodgett Memorial Hospital in

Turnover at CEQ

Two new members have been sworn in on the Council of Environmental Quality (CEQ) to replace Robert Cahn and Gordon J. F. MacDonald, who have resigned. They are Beatrice E. Willard, president of the Thorne Ecological Institute of Boulder, Colorado, and John A. Busterud, deputy assistant secretary of defense for environmental quality.

Willard, 47, will be the scientist as well as the woman in the CEQ triumvirate. An ecologist educated at Stanford and the University of Colorado, she taught biology at South Oregon College for a year before joining the institute as executive director in 1965. Thorne Ecological Institute, founded in 1954, is an educational organization that does applied research for private industry and supplies advice on how companies can conduct their operations in a manner harmonious with environmental considerations.

She is also the author of several books on alpine ecosystems and has served on a number of Colorado state committees concerned with the environment. She is, among other things, chairman of the Sierra Club's Rocky Mountain chapter.

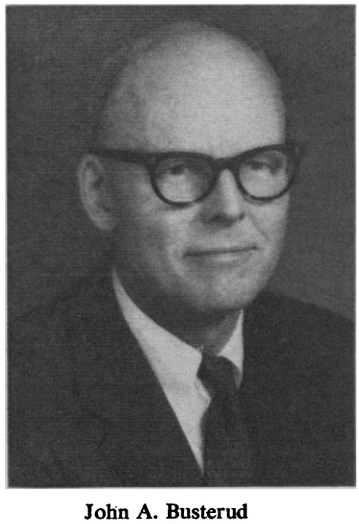
The Administration's eagerness to get Willard on board is evinced by the fact that they started pursuing her in May. But it was not until August that she decided that the institute, something of a "one-man" operation, could survive without her.

Busterud, 51, is a lawyer, conservationist, and native of Oregon. Before coming to Washington in 1971, he was a senior partner in a San Francisco law firm specializing in conservation and antitrust law. His was the first appointment to the Defense Department post that was created by Secretary Melvin Laird to help the military conform to the aims of the National Environment Policy Act. Busterud's office has been working on "getting the military to think environmental quality" from early planning stages onward, and it reviews environmental impact statements on controversial matters such as the storage and disposal of the phased-out Herbicide Orange.

Busterud is frankly "thrilled" at his new job at CEQ, which he sees as "the environmental conscience of the nation."

As for the pair who left the council, Cahn has returned to his job on the *Christian Science Monitor*, and MacDonald is director of the Environmental Studies Program at Dartmouth College. Last month MacDonald was also named chairman of the Environmental Studies Board of the National Academy of Sciences.—C.H.

Beatrice E. Willard



John A. Busterud

Grand Rapids was not entirely original —urea had been identified before as an agent that reverses sickling—but he was the first to develop a clinical protocol for administering urea in sugar solution to patients during a sickle cell crisis. After trials on more than a dozen patients, Nalbandian enthusiastically reported that urea was bringing people out of crisis faster than other therapies. His reports, which were based on uncontrolled studies, stirred up considerable controversy and he drew the wrath of many of his medical colleagues, who were appalled by the amount of attention his ideas were getting in the press. Today, investigators at several centers are conducting controlled studies of urea therapy with support from the NHLI program. Nalbandian is not among them.

In vitro, cyanate prevents sickling in concentrations much lower than those required to get any effect with urea, according to Anthony Cerami, James M. Manning, and their colleagues at Rockefeller University. Clinical trials of potassium cyanate are also planned. But in spite of the hope that has been generated by this work, many investigators remain skeptical of its ultimate therapeutic value. Few predict that either urea or cyanate will prove to be the best means of relieving sickle cell crises.

Another approach to the problem of bringing patients out of painful crises is based on the premise that there is a cofactor necessary for the induction or enhancement of crisis. Murayama, for example, is convinced that such a cofactor exists and has been struggling to isolate it. His work, he has claimed, is hampered by lack of support.

Pauling and associates of his at the Stanford University Medical Center also support the cofactor hypothesis and have gone so far as to propose what it is. Pauling and Paul L. Wolf, an M.D., have a grant of $92,000 from the NHLI to study prostaglandins in relation to sickle cell anemia. In a paper that will be published in *Clinical Chemistry*, Wolf and others suggest that prostaglandin E_2 can induce sickling under conditions of reduced oxygen tension. They arrived at this hypothesis, Wolf says, when they realized that during pregnancy and infection, two conditions known to precipitate sickle cell crises, prostaglandin E_2 levels rise. "We think it is possible that, if you can affect E_2, you can control sickle cell crises," Wolf says. Like other postulated methods of handling patients in crisis, this too has yet to be proved.

In spite of all the controversy that the national program to combat sickle cell anemia has generated with regard to screening and to therapy, persons active in the area have come to the conclusion that the positive features outweigh the negative by far. Pearson, for example, believes that one of the most important effects of the program may really be a side effect of sorts. The emphasis on sickle cell anemia, as he sees it, has made the black community far more aware of health problems in general. "We may be able to capitalize on this to get people interested in nutrition and immunization against polio and diphtheria and the like," he says.

Scott thinks that one of the primary benefits of the sickle cell program, in addition to whatever it may bring patients, will be to open doors for black people interested in getting into medicine, as physicians, nurses, technicians, or other categories of health professionals. He would like to see federal money go to black scientists and, especially, to the university medical schools at Howard and Meharry, the only two institutions with a "black identity." So far, he says, "this has not happened to the maximum extent." But Scott, an optimist, believes that, with persistence, things will change and that, when the current national fascination with sickle cell anemia declines, as he believes it will, the wave of interest will, nonetheless, have left behind a solid new base for recruiting and training black people in science.

—BARBARA J. CULLITON

SIPRI: Peace Research Institute Losing Old Staff, Pondering Role

World military spending now runs about $200 billion a year—say $50 for each man, woman, and child alive. What this cheerless statistic has to say about the character of man and the nature of international relations is the starting point for peace and conflict research, a newish discipline that is growing rapidly, if not yet quite as rapidly as its subject of study.

One of the first institutions in the field, and still perhaps the best known, was the Stockholm International Peace Research Institute (SIPRI). Despite its name, it eschews the wilder shores of peace research: indeed, its painstaking techniques of gathering and publishing information seem today almost old-fashioned. Set up in 1964 to celebrate Sweden's 150 years of peace, SIPRI is proving an enduring monument to the stolid pragmatism of the Swedes, and —so its supporters believe—its virtues of reliability and political detachment may well prove longer lasting than other, more fashionable approaches.

Although SIPRI emphasizes its internationalism, it takes much of its style from Alva and Gunnar Myrdal, the two Swedes who were instrumental in setting it up. Alva Myrdal, first chairman of SIPRI's Governing Board, was succeeded by her equally distinguished husband when she became Sweden's disarmament minister. Gunnar Myrdal declares that he can see no reason why political problems cannot be dealt with in a scientific way. "The principle is to carry out cold-blooded, hard research, based on published sources," he says. "Our value-premise is a simple one: it is to prevent war and preserve peace."

What this philosophy has produced in practice is a staff of around 15 researchers dedicated to the proposition that human beings are ultimately influenced by the truth, simply and straightforwardly told. The bulk of SIPRI's work consists of careful digging through masses of military information, sorting out fact from propaganda, and preparing collections of the information thus gathered. Only public sources are used—SIPRI is not in the intelligence