Blood Diseases Partially Corrected by Gene Alteration

In a major advance in human gene engineering, three patients with beta-thalassemia and three patients with sickle cell anemia have had their diseases partially corrected by gene manipulation. The feat may also result in an effective treatment for these two severe types of anemia. At present both are serious, incurable, inherited blood diseases.

The three beta-thalassemia patients and two of the three sickle cell anemia patients were treated by Timothy J. Ley, Arthur W. Nienhuis and colleagues at the National Heart, Lung and Blood Institute in Bethesda, Md. and by Joseph DeSimone and Paul Heller of the University of Illinois College of Medicine in Chicago. The remaining sickle cell anemia patient was treated by George Dover, Samuel Charoche and Kirby Smith of the Johns Hopkins Medical Institutions in Baltimore. Ley and his colleagues reported their results in the Dec. 9 NEW ENGLAND JOURNAL OF MEDICINE. Dover and his co-workers presented theirs at a meeting of the American Society of Hematology in Washington in early December.

Hemoglobin in red blood cells is normally composed of amino acid chains called alpha globins and amino acid chains called beta globins. In beta-thalassemia, a gene that codes for beta globins is defective so that beta globins are deficient or absent. As a result, a relative excess of alpha globins is formed. This excess interferes with normal red blood cell formation, creates severe anemia and can lead to death. Researchers, then, have been eager to find some way of correcting the relative excess of alpha globins in beta-thalassemia patients and thus countering their disease.

Studies during the past 15 or 20 years have suggested that the answer might lie in another kind of globin called gamma. Usually gamma globins are expressed in large amounts during fetal life only. Yet gamma globins are known to be capable of combining with alpha globins to form hemoglobin. Thus scientists conjectured that they might be able to increase the production of gamma globins in beta-thalassemia patients. And if so, the gamma globins would combine with the excess alpha globins, and the excess would no longer be available to cause disease.

Research of the past two or three years has hinted at how gamma globin production might be stepped up in beta-thalassemia patients. This would be with a drug called 5-azacytidine. The reasons are that gamma globin genes appear to have few methyl groups attached while making globins, and that 5-azacytidine seems to be capable of removing methyl groups from genes. The drug 5-azacytidine, scientists reasoned, might be capable of increasing gamma globin production in beta-thalassemia patients. DeSimone and Heller gave 5-azacytidine to baboons to see whether it could increase their gamma globin production. It could, they reported in the July PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES.

Then, with Ley and his colleagues, they gave 5-azacytidine to three beta-thalassemia patients for a week to see whether it would increase their gamma globin production, whether the gamma would combine with their excess alpha, and whether a reduction in alpha would lead to better red blood cell formation and less anemia. They succeeded on all four counts, they reported in the Dec. 9 NEW ENGLAND JOURNAL OF MEDICINE.

Another rationale prompted them, as well as Dover and his colleagues, to give 5-azacytidine to three sickle cell patients. In sickle cell anemia, beta globins contain an incorrect amino acid and form abnormal hemoglobin molecules. The abnormal hemoglobins distort red blood cells into a sickled shape. The hope, then, was that 5-azacytidine might increase gamma globin-type hemoglobin in sickle cell patients, and such an increase would reduce the ratio of abnormal beta-type hemoglobin and in turn the number of sickled red cells. Here, too, the investigators succeeded.

These results are "very exciting," attests Yuet Wai Kan of the University of California at San Francisco. Kan and his colleagues succeeded last spring in increasing beta-globin production in frog eggs by using another form of gene manipulation (SN: 5/1/82, p. 292). In an editorial in the Dec. 9 NEW ENGLAND JOURNAL, Edward J. Benz Jr. of Yale University School of Medicine writes: "The studies of Ley and Dover and their colleagues represent the first encouraging attempts to achieve clinical management of gene expression by molecular manipulation of DNA *in vivo*."

In an interview, however, Nienhuis cautioned that it is too early to know whether 5-azacytidine will pan out as a successful treatment for the two blood diseases because patients got it only for a short time and its ideal dosage remains to be determined. And as Kan points out, "The drug has to be tested to see if it has any long-term side effects."

—J.A. Treichel

Clark survives broken heart

The world's first artificial heart recipient — 61-year-old Barney Clark of Seattle — has been described as a "rugged Rocky Mountain sagebrush." And as of two weeks after his heart implant, this description appeared to be apt. He had endured not just the implant while dying from heart disease, but also a subsequent operation for a lung complication unrelated to the artificial heart (SN: 12/11/82, p. 372) and yet a third operation to correct a malfunction in the heart itself.

Wide World

Jarvik explains valve failure in Clark's artificial heart.

The complication that set the stage for this third operation appeared on Dec. 14. Clark's blood pressure plunged drastically, implying that the heart wasn't working right. Doctors rushed him into the operating room at the University of Utah Medical Center in Salt Lake City, where he has been staying since his heart implant of Dec. 2. He was maintained on a heart-lung bypass machine while his artificial heart was examined and worked on. Doctors found the mitral valve connecting the left ventricle of the artificial heart to Clark's natural left auricle had broken, causing blood to regurgitate back into the auricle. The doctors pulled out the faulty left ventricle and replaced it with a spare one. Clark was taken off the heart-lung bypass machine; he depended on the artificial heart for survival. Once again it functioned normally.

Robert K. Jarvik, the University of Utah bioengineer who designed the heart, said he wasn't sure why the valve fracture developed. The artificial heart was known to put considerably more pressure on the mitral valve than a natural heart would; Jarvik and his colleagues had had mitral valves in artificial hearts break while testing them on animals (SN: 3/7/81, p. 157), and at least one animal died because of a valve break.

After the heart valve operation, Clark was very sick and had developed pneumonia. However, by Dec. 15, his pneumonia had responded to antibiotics, and as of Dec. 16—exactly two weeks after he received his artificial heart — he was still in critical condition but slowly improving.

—J. A. Treichel