Hemophilia Gene Found

The clotting factor missing from the blood of most hemophiliacs might be produced synthetically, say researchers at a Boston-based biotechnology firm. The scientists announced this week they have discovered and cloned a piece of the gene responsible for producing the substance.

Though leading hematologists hailed the finding of the gene for "Factor VIII" as an important first step, they cautioned patients that several years and a few research roadblocks must be traversed before the refined protein is available at their local drugstore.

"Until we had a piece of the gene, we were more or less groping. Now we have a start," says Jay Toole, the biologist at Genetics Institute, Inc. who headed the project. Toole predicts the artificial clotting factor might be available for testing in patients in two to five years.

At least a half-dozen research teams have raced for more than two years to identify and clone the gene for Factor VIII, a chemically unstable protein present in trace amounts in the blood. Hemophiliacs with the most common form of the disease make little or no Factor VIII, and are subject to bleeding that can be crippling or fatal if uncontrolled. While bleeding can be stopped with transfusions of Factor VIII skimmed from donated blood, the treatments are expensive—typically $5,000 to $10,000 a year per patient—and risky. The form of the protein most commonly given comes from blood plasma pooled from thousands of donors, making the risk of contracting the blood-borne hepatitis B virus extremely high.

In addition, the Centers for Disease Control in Atlanta reported this week that a total of 21 cases of Acquired Immunodeficiency Syndrome (AIDS) have occurred among hemophiliacs since 1981, amplifying concern that whatever causes AIDS might be transmissible through blood transfusion (SN: 1/1/83, p. 8). Alan Brownstein, executive director of the National Hemophilia Foundation, emphasizes that the risk of death to the 20,000 hemophiliacs in the United States, from untreated hemorrhaging is much greater than the possible risk of contracting AIDS through transfusion. Nonetheless, the added safety against all types of infection that a purer synthetic version of Factor VIII could provide would be an important advantage, he says. Other advantages would be increased availability of the protein — especially in developing countries where prohibitive cost means many hemophiliacs are never treated—and, potentially, a reduced unit cost of the factor for all patients, he says.

But several steps must be completed before such a protein could be produced. Toole and colleagues John Knopf and John Wozney have cloned a fragment of the gene that humans use to make the protein, and expect to identify and clone the complete gene within six months. Whether such a gene could be inserted in bacteria or yeasts and harnessed to produce large quantities of usable protein on a commercial scale has yet to be determined.

Relatively little is known about the structure and biochemical activity of natural Factor VIII, Toole says, so it is difficult to predict whether bacteria, yeast or mammalian cells would be the best host for producing the synthetic protein.

"This is an important finding, and it's very encouraging," says W. French Anderson, a molecular geneticist in hematology at the National Institutes of Health in Bethesda, Md. "But there is still a long way to go before recombinant DNA Factor VIII can be commercially available."

Baxter Travenol Laboratories of Deerfield, Ill., owns 6 percent of Genetics Institute and was a co-sponsor of the project.

—D. Franklin

New Factor in Salt?

A long-held medical belief—that sodium is the component of salt responsible for increasing blood pressure—deserves a second look, say University of California at San Francisco researchers.

In a paper in the Dec. 9 SCIENCE, and another presented this week before the American Society of Nephrology, Theodore W. Kurtz and R. Curtis Morris Jr. report that rats' blood pressure increased to a much greater extent following ingestion of sodium chloride (salt) than following ingestion of other sodium compounds. This indicates, Kurtz and Morris say, that sodium alone may not be the culprit, and that chloride plays a more active role than had been thought.

While limiting salt intake to prevent high blood pressure—hypertension—is a topic of debate (SN: 4/9/83, p. 233), salt's role in hypertension is firmly established. People with high blood pressure are told to limit their intake of sodium—no mean trick because sodium is a hidden ingredient in most processed foods.

In the early part of this century, chloride was considered the villain. But especially in the past three decades, sodium has been implicated. "There's been a general feeling that sodium is related to hypertension through some function of blood volume," says Morris. "People had just gotten fixed on sodium—more was known about it earlier." Sodium is actively pumped in and out of cells, affecting the cells' activity, so a dynamic role seemed reasonable.

Morris noticed that patients given large amounts of sodium bicarbonate to treat a kidney problem got edema—swelling of the tissues — but not hypertension, and decided to take a closer look at sodium.

He and Kurtz induced hypertension in 41 rats by removing one kidney from each and then feeding them desoxycorticosterone, a naturally occurring hormone that promotes sodium and chloride retention. Rats that received sodium chloride in amounts usually occurring in a laboratory diet had "significantly greater" blood pressure rises than rats given an equivalent amount of sodium in sodium ascorbate, sodium bicarbonate or both.

"The difference began at two weeks and persisted over the five weeks the study was carried out," Kurtz says. The results could not be explained by changes in weight or food intake. Their conclusion: "Given the sketchy understanding of nutritional factors...it seems prudent to speak of sodium chloride-dependent hypertension rather than 'sodium-dependent' hypertension."

The researchers have yet to test the effects of chloride alone. "It's somewhat difficult to find such compounds," says Kurtz.

The study results surprised several clinicians. Says Norman Kaplan, a high blood pressure specialist at the University of Texas Health Science Center in Dallas, "It seems all the experiments have been on salt." Recent studies have shown that potassium chloride lowers blood pressure, he notes. "That would be indirect evidence that chloride is not a culprit per se." But, he notes, chloride could promote sodium's effects. Edward Freis of the Veterans Administration Medical Center in Washington, D.C., is more doubtful. "Almost all the human patients with high blood pressure are sodium-dependent," he says. "The evidence is pretty solid."

The California researchers are not yet ready to suggest a mechanism describing how chloride might exert an effect on high blood pressure. Active pumping of chloride across cell membranes has recently been described, and they speculate that such a pump may affect the activity of cells in smooth muscle tissue.

—J. Silberner