Finding and treating genetic diseases

Newly discovered birth defects are aided by massive vitamin dosage

No one knows how many genetic diseases afflict man. As methods of studying human biochemistry take on new sophistication, scientists find themselves reluctantly adding names to the already long list of inherited disorders. Indeed, it has been estimated that as many as a quarter of all illnesses have a genetic component, although they are by no means all directly heritable.

Of the more than 100 human diseases that are known to be passed directly from parents to children, very few are treatable at all. Therefore, when a geneticist finds himself in the position of reporting a new heritable disease and can, at the same time, announce that something can be done about it, it is a source of satisfaction.

This happy fate has befallen Dr. Leon E. Rosenberg of Yale University, one of a comparatively small number of medical geneticists in the United States whose research focuses on vitamin-dependent genetic diseases.

The first of these derangements was identified in 1954 when Dr. Andrew D. Hunt observed that enormous doses of vitamin B_6 relieved convulsive seizures in two infants. Since that time, 40 cases of genetically determined B_6-responsive seizures have been documented. And since that first report the list of vitamin-dependent genetic diseases has grown to nearly a dozen (four were added last year alone), including metabolic errors responsive to vitamins D, B_1, B_2, B_6 (five distinct disorders) and B_{12}.

Dr. Rosenberg discussed this special class of inborn errors of metabolism this month at a seminar on medical genetics in Bar Harbor, Me. The meeting was sponsored jointly by the Jackson Laboratories and Johns Hopkins University with the support of The National Foundation—March of Dimes.

Drawing a distinction between vitamin-dependent diseases and vitamin deficiencies such as scurvy and pellagra, Dr. Rosenberg points out that the latter can be treated with small doses of vitamins whose absence from the diet caused the diseases in the first place. Vitamin-dependent disorders, on the other hand, require continuing and massive doses of a specific vitamin and occur not because the patient lacks normal levels of the vitamin in question but because his body is unable to use it properly, if at all. Therapy may demand from 10 to 1,000 times the usual vitamin requirements.

Vitamin-dependency diseases, identified altogether in fewer than 100 persons to date, are generally detected by the presence in serum and urine of abnormally large quantities of some chemical. Thus, in homocystinuria, for example, patients have high levels of homocystine. Clinically, these patients may be mentally retarded and suffer from osteoporosis and dislocation of the lenses of the eyes.

AMA

Rosenberg: Time to start looking.

Treating several homocystinurics with a massive regimen of vitamin B_6, Dr. Rosenberg found he could correct the biochemical defect; homocystine levels could be returned to normal. But the symptoms of the disease were irreversible.

"In all likelihood," he speculates, "that is because the youngest patient we treated was 15 years old and the damage had been done. However, if we could detect homocystinuria at birth, we might be able to prevent that damage."

It is estimated that homocystinuria may occur in one of every 20,000 individuals, making it as common as phenylketonuria (PKU), a metabolic error for which most newborns are now routinely screened. Says Dr. Rosenberg, "To my knowledge, Massachusetts is the only state in which newborns are routinely checked for homocystinuria. It is a very progressive state in that regard."

The other known vitamin-dependency diseases are probably far less common, although until more physicians begin looking for them, no one can say with certainty. Pediatricians, Dr. Rosenberg believes, should start looking, especially when they see an infant with unexplained protein intolerance, acidosis or a general failure to thrive. "I am concerned," he says, "that every year in every hospital there are children who die because they are afflicted with some of these metabolic diseases that are never detected."

At the same time, the Yale doctor emphasizes that vitamin therapy is "not a cure-all for all metabolic diseases," and stresses that while no toxicity from massive B-vitamin therapy has been found so far, the effects of prolonged dosing have yet to be evaluated. Clearly, some vitamins, such as A and D, can be dangerous. They are fat soluble and tend to accumulate in body tissue. Vitamins B and C, however, may present less danger because they are water soluble. The kidneys excrete any excess the body does not use.

Studies of these vitamin-dependent abnormalities, in addition to obvious clinical value, have shed light on the roles normally played by vitamins. Says Dr. Rosenberg, "It is clear that most, if not all, vitamins serve as coenzymes to facilitate a variety of metabolic processes." Enzymes are the protein catalysts that speed all biochemical reactions, generally through a complex sequence of events. Instead of acting directly on a substrate (chemical to be metabolized), enzymes enlist the aid of coenzymes or cocatalysts. By virtue of their molecular structure, these molecules provide an active site with which the substrate can react, building an intermediate molecule with which an enzyme will, in turn, react.

Essentially, vitamin-dependent disorders, like all inborn errors of metabolism, involve an enzymatic disturbance. In many of the genetic vitamin diseases described thus far, a disturbance in vitamin–coenzyme functioning may be the faulty mechanism.

There are, Dr. Rosenberg suggests, three possible biochemical defects involved in vitamin-dependency diseases. In some instances the specific defective mechanism is understood; in others it is not.

First, the defect may lie in a partial

block in the mechanism of transporting vitamins across membranes and into cells in the body. When this is the case, massive doses may work by so saturating the exterior cellular environment that there is enough vitamin to get through. Second, an intracellular inability to break vitamins down, converting them to coenzymes, may be at fault. Third, there may be an abnormality within the cell in apoenzymes, proteins which hook up with vitamin coenzymes to form an active unit which interacts with cellular enzymes.

In a vitamin B_{12}-responsive disorder known as methylmalonic aciduria, conversion appears to be the defective mechanism. Biochemical studies of a child diagnosed with this condition at eight months of age confirm this hypothesis. Clinical treatment with 1,000 micrograms per day (the normal requirement is less than one microgram per day) appears to substantiate the validity of vitamin therapy. At eight months the child was underweight and showed signs of slow mental development. A year later, his weight and mental growth were normal.

The mechanism by which vitamin B_6 reverses the biochemical defect in homocystinuria is thought to be somewhat different and is one that raises both hopes and problems. Unlike true enzymes which are highly specific in their reactions—presumably each enzyme in the body performs but a single function—vitamin coenzymes operate in a variety of metabolic processes. Vitamin B_6, for example, plays a role in several unrelated metabolic events. In homocystinurics, Dr. Rosenberg suggests, massive B_6 doses act not by correcting or overwhelming the defective metabolic pathway but, by virtue of their versatility, by opening a new one. In effect, the doses create a new channel in which the necessary biochemical reactions can take place.

Says Dr. Rosenberg, "This hypothesis should infuse an extra measure of caution into the experimental treatment of homocystinuria. It is one thing to activate a normal enzymatic process that for one reason or another is failing to function, as in methylmalonic aciduria. It is something else again if, in the course of treatment, we open an alternate, normally inactive process. While doing so might correct the immediate biochemical abnormality, it might also generate abnormalities on its own."

With that caution duly taken, it is also possible that by deliberately activating nonfunctional metabolic pathways, scientists may be able to one day correct a host of metabolic disorders by using drugs specifically tailored to unblock unused metabolic routes. For this, vitamins are a model and a beginning. □

DUBRIDGE LEAVES

New man for Nixon

Since the post was created under President Eisenhower, the Science Adviser to the President has been either a physicist or a chemist. Now for the first time an engineer will hold the job. President Nixon has appointed Dr. Edward E. David Jr. of Bell Telephone Laboratories to be Science Adviser and has nominated him to the companion post of Director of the Office of Science and Technology. (The latter post requires confirmation by the Senate; the advisership does not.)

Dr. David, whose work has been mainly in the fields of computers, cybernetics and communications theory, is executive director of communications research at Bell Labs.

The 45-year-old engineer will succeed Dr. Lee A. DuBridge, former president of California Institute of Technology, who has held the joint position since the Nixon Administration assumed office. In tendering his resignation Dr. DuBridge cited his age —he will be 70 next year—as a ground for retirement. He also mentioned his disappointment at the amounts of money being appropriated for science. In his letter to Mr. Nixon, he blames Congress for not voting all the money asked by the President.

Scientists outside the Government tend to blame the Administration for the lack of funds. In their view the amounts the President asked for are insufficient. Budgets of most Government agencies that fund science are down. Some government laboratories are closing; others are discharging employes. There is less money for research grants.

All this has caused a depression in the pure sciences that is particularly severe for physicists, but is being felt by all categories of researchers. Many see the decline as expressing a Government policy of decreasing the nation's effort in pure science. Since the scientists generally regarded Dr. DuBridge as their ambassador to the White House, he had been hearing more and more expressions of their discontent in recent months. Some of the scientists felt that he has been more concerned to justify Administration policy to them than to express their anguish to the President.

Appointment of an engineer to succeed Dr. DuBridge seems to mean that the policy, if it is a policy, is likely to continue. Dr. David says the President feels science should be used for the benefit of people. In statements that he has made so far Dr. David has emphasized such things as health services, transportation, defense and housing. According to White House officials some of the things the President is particularly interested in are treatments for cancer, heart disease, emphysema and dental caries.

Bell Labs

David: Advice from a cyberneticist.

Two of the Government's highest scientific officials have responded to the appointment with expressions of welcome. Dr. H. E. Carter, chairman of the National Science Board, says, "The board looks forward to a continued close relationship between the National Science Foundation and the Office of Science and Technology under Dr. David's direction. As a former member of the Foundation's Advisory Committee for Engineering, Dr. David is already familiar with the Foundation's role in the Federal support of science and its utilization for the betterment of mankind."

Dr. William D. McElroy, director of the National Science Foundation, says the appointment means "continuing progress in the development of Federal science policy."

The reaction of nongovernment scientists is less enthusiastic. Although Dr. David is a member of both the National Academy of Sciences and the National Academy of Engineering, few scientists seem to know him. Says one: "DuBridge is, well, conservative, but he was President of Caltech, and nobody could object to that."

Another remarks, "I understand the main criterion was that he [David] be a full-blooded Republican."

Says Dr. Jeremy Stone, executive secretary of the Federation of American Scientists, "I am concerned that the office of science adviser might gradually become diminished in prestige through the appointment of scientists who are not well known to the scientific community."

Dr. David is scheduled to take up his duties Sept. 1. A spokesman for the Senate Committee on Labor and Public Welfare says the committee will probably not get to confirmation hearings until after Labor Day. □