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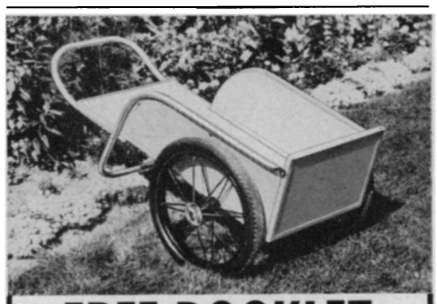

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MOLECULAR BIOLOGY

Inherited Diseases: On The

Defective enzymes give scientists clues to diseased and normal life functions.

by Barbara J. Culliton

Inherited diseases that plague families for generations will one day be wiped out, scientists now predict.

Cancers that run wild when a cell's biochemical controls break down will also be stopped short.

Already doctors can sometimes spot heart disease and hepatitis before any symptoms appear.

These and other advances are possible because scientists are unraveling the intricate secrets of enzymes that trigger the 100,000 or so biochemical reactions that keep the body in working order.

Enzymes interpret the genetic code every individual inherits from his parents and carry out the orders genes give for growth and development.

When a gene wants something done, it produces a specific enzyme to do it. Occasionally, faulty mutant genes make defective enzymes, and when this happens, something is likely to go wrong.

For example, phenylketonuria or PKU is a genetic defect causing some 400 American babies a year to become idiots and imbeciles. PKU victims are born without an enzyme called phenylalanine hydroxylase which is necessary for the metabolic conversion of one amino acid, phenylalanine, to another, tyrosine. Because the enzyme is missing, PKU patients fail chemically to change phenylalanine to tyrosine. Instead, they build up excesses of phenylalanine which hinder normal mental development.

Now, a simple test measuring phenylalanine levels in urine enables doctors to diagnose PKU at birth. By instituting special diets—no meat or dairy products—immediately, some cases of mental retardation are avoided. However, dietary restrictions are by no means a sure cure.

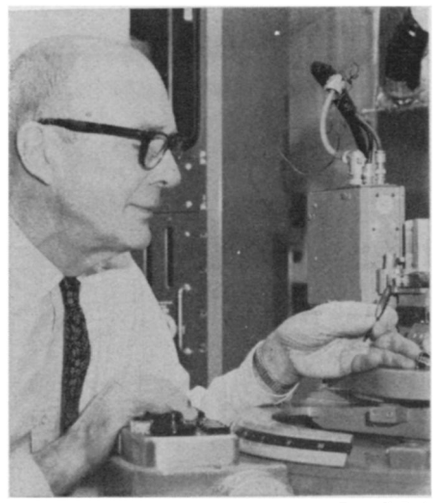
Recently, 36 states passed laws requiring PKU enzyme tests for every newborn, although some researchers challenge the wisdom of such laws. "We may be doing as much harm as good," says Dr. Samuel Bessman of the University of Maryland, who fears the laws give the false impression that doctors already know all there is to know about PKU (SN: 12/24/66).

Eventually scientists hope to eradicate this inherited disease by replacing the defective enzyme, or more revolutionary still, by eliminating the defective gene and substituting a normal gene before it is passed on from parent to child.

The mystery of enzymes is unfolding in a pop art of abstract designs and complex models as researchers take to the drawing board to picture the structure of enzymes.

So far, detailed blueprints map the architecture of three vital enzymes:

• In the 1950s British scientist Dr. John C. Kendrew used X-ray crystallography to decipher the structure of myoglobin, the muscle protein that stores oxygen.



Roswell Park

Dr. Harker: 16 years on one protein.

• In 1965 Dr. David C. Phillips and his colleagues at the Royal Institution in London defined the three-dimensional character of lysozyme, an enzyme composed of 129 amino acids that bores into bacteria and breaks them open.

• Most recently, Dr. David Harker of Roswell Park Memorial Institute, Buffalo, N.Y., drew a blueprint of ribonuclease, the enzyme that deactivates RNA or ribonucleic acid.

The use of X-ray crystallography and computers in unlocking enzyme structure is now firmly established. Dr. Harker who spent 16 years defining the structure ribonuclease, predicts the three-dimensional structure of other enzymes can be described in only five to ten years time or even less.

Enzymes, like all proteins, are made up of amino acids that line up one after the other in a highly specific sequence dictated by a gene. But working enzymes are not linear arrays. Once all

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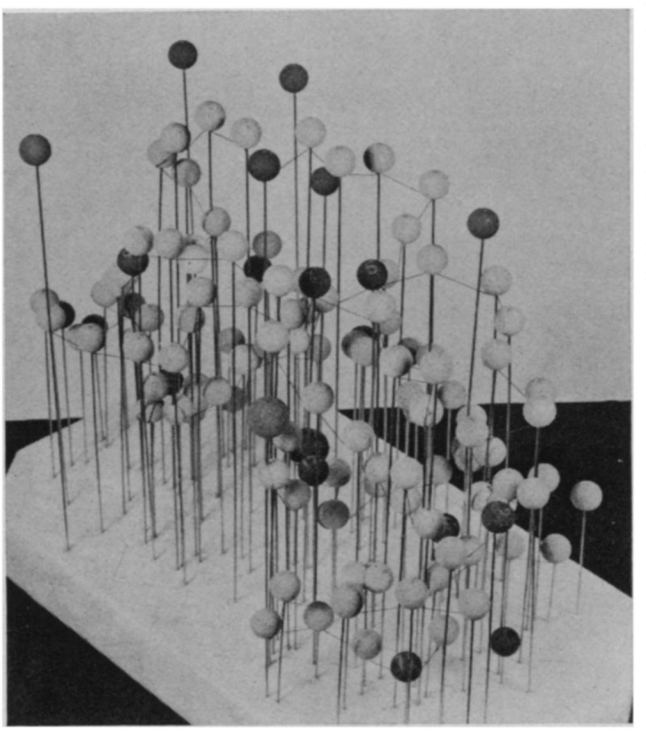
Way Out

the amino acids are in place, the enzyme folds itself into a coil or helix, because certain of the amino acid molecules with a special affinity for each other are drawn together. If even one of these molecules is out of place or missing, the enzyme's shape and ability to catalyze chemical reactions may be seriously altered.

If you build an arch with 129 finely shaped stones but put one of them in upside down, you'll warp the arch. So it is with enzymes. In order to function as catalysts, a specific, though yet unknown site on the enzyme has to come in contact with an amino acid or other target compound; all are known as substrates. Here it's a matter of form and function depending on each other. Each enzyme has a cleft into which its substrate fits like pieces of a jigsaw puzzle. In this situation a structural deformity in the enzyme can be lethal to the cell.



Although enzyme synthesis is scientists' goal, no protein except insulin has been synthesized yet. "Enzymes can't be easily synthesized because they're so big," says Dr. R. G. Denkewalter of the Merck Institute, Rahway, N.J. "And even if we could synthesize them, we're not sure just what we'd do with them. Many enzymes operate inside cells, and we have no way of injecting anything directly into a cell in the body."

But Dr. Denkewalter and others are working on enzyme synthesis "because the challenge is fun" and because understanding of enzyme structure gives important clues to how enzymes work.

Until now time has been a major hindrance to structure studies of enzymes and all proteins. In order to make the first step in structure analysis, chemists must figure out the amino acid sequence of the enzyme. Taking an enzyme apart bit by bit using only hand methods can easily take somewhere in the neighborhood of 10 years.

But now, from Australia Dr. Par Edman reports development of a remarkable robot chemist (SN: 7/19). His new machine, called a protein sequenator, splits proteins apart using the usual array of reagents and solvents to isolate each individual amino acid molecule; and it does it automatically, handling up to 15 amino acids a day, instead of a chemist's two or three, and reducing protein analysis to a matter of days, not years.

The genetic revolution now going on was started in 1902 when Sir Archibald Garrod published in LANCET a paper with the unrevolutionary title, "The Incidence of Alcaptonuria, a Study of Chemical Individuality." Alcaptonuria, a rare disorder in which urine turns black, is an enzyme deficiency inherited as a recessive Mendelian trait. Mendel was the 19th century Austrian monk who first studied genetic inheritance and discovered traits passed on through dominant and recessive genes.

Alcaptonurics lack an enzyme called homogenestic acid oxidase. "The disorder has some effects on cartilage and nearly always leads to arthritis," Dr. Frederic C. Bartterr of the National Institutes of Health, Bethesda, Md., explains.

Garrod's insight into genetic deficiencies went largely unnoticed until the 1950s when Nobel Prize winner Dr. George Beadle clearly stated what Garrod and others had implied; namely, for one gene there is one enzyme. And though some of Garrod's conclusions have been modified since, his general hypothesis explaining what happens when an enzyme is absent or doesn't function still holds.

Garrod described the concept of a metabolic pathway in which substances are converted in a series of stepwise reactions. When one enzyme fails to carry out its share of the work, the pathway is blocked.

Theoretically, there are two ways to clear things up. Either replace the defective enzyme, which is presently impossible if that enzyme is inside a cell, or supply the end product the body fails to make when metabolism is altered. Where this is possible, it works fairly well.

In hemophilia, for example, patients (usually men who have inherited the sex-linked recessive gene from their mothers) lack antihemophilic factor oxidase, an enzyme. Transfusions of plasma rich in antihemophilic factor are successful treatment; a case of supplying a missing end product—treatment, not cure.

Modern geneticists, however, place more and more emphasis on cure rather than treatment in their efforts to get at the root of human disease and understand normal life processes.

Sophisticated techniques for identifying and studying enzyme activity are turning up rapidly, and with them doctors are spotting increasing numbers of inherited diseases. Although these new diseases are not always significant in terms of the numbers of persons they afflict, they offer an opportunity to identify new metabolic pathways and new enzyme activities in clinical investigation.

Most recently Dr. Roscoe Brady and his associates at NIH identified the sex-linked enzyme deficiency responsible for Fabry's disease that attacks heart, kidneys, central nervous system, skin and eyes. Another disorder, called sulfite oxidase deficiency, was spotted for the first time in a two-year-old boy whose three brothers and sisters died within a month of their births, probably of the same inherited defect (SN: 7/1).

Where there were once perhaps a dozen known enzyme diseases, there are now more than a hundred with cancer leading the list in some scientists' view. Even migraine headaches have been linked to defective enzymes.

In heart disease and hepatitis among other diseases, enzymes are used as a diagnostic tool, sometimes pointing up disorders before patients realize they're sick. Lactate dehydrogenase, an enzyme with five specific known forms, was first identified as a clinical tool in 1958 by Dr. Elliot Vesell of NIH. Too much LDH 1 in serum is an indicator of myocardial infarction or heart disease. LDH 2 is high in leukemia patients and LDH 5 signals hepatitis.

With patients, insight and interest multiplying at an explosive rate, scientists are confident they'll learn how enzymes work in a couple of decades.