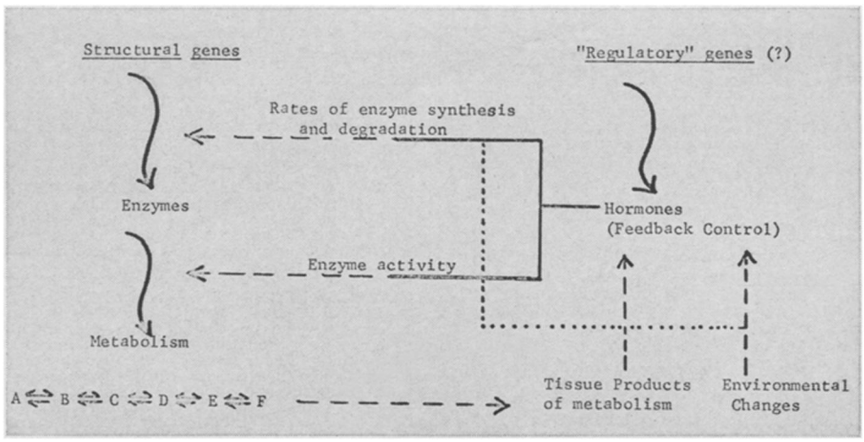
BIOCHEMISTRY

Frontier: Genetic control

Emphasis shifts from gene structure to gene function

by Barbara J. Culliton



Jackson Lab

Regulatory genes, as well as structural genes, may have a role in metabolism.

There is a saying among biologists that what is true of the bacterium is true of the elephant. The language of life is universal, coded in genes that are fundamentally alike in all living cells. Unraveling the structure and alphabet of genetic molecules has been, for more than a decade, the foremost of scientific pursuits. To a large extent, that job is done, and several Nobel Prizes have been won for its doing.

Now, the focus of genetic and biochemical research is turning to the refinements that make the bacterium and the elephant different. Scientists are being challenged to explain the control systems that regulate the decoding of genes and ultimately account for the fact that simple bacterial cells and highly complex mammalian cells are products of the same genetic material.

At this juncture, illumination of mammalian control systems is the key and the problem; bacterial systems are far simpler, experimentally far easier, to approach. But extrapolation of data from bacteria to mammals is risky.

"Mammalian cells," Dr. James B. Wyngaarden of Duke University noted at a recent Bar Harbor symposium on Genetic Control of Mammalian Metabolism, "are infinitely more complex. Compared to bacterial cells, they have 1,000 times more of everything.

"Some understanding has been gained of the mechanism regulating gene expression in bacteria," he says. "Information on the mechanism regulation in mammalian cells is much more limited, but progress is sufficient to indicate that there are important differences in the control identified in bacteria and higher organisms."

"The task," according to Dr. Earl Green, director of the Jackson Laboratories in Bar Harbor, Me., sponsor of the meeting, "is to map, in precise molecular terms, the way in which genes bring about their effects. One way to try this is to tackle the evolution of a single enzyme."

But even that is far from simple. In order to understand the cumulative genetic factors involved in the development of a single working enzyme, says Dr. Kenneth Paigen of the Roswell Park Memorial Institute in Buffalo, scientists still have to know:

- The stages of development at which it appears and disappears.
- Its location within the cell. (While bacterial enzymes occur randomly within the cells, mammalian enzymes are located in specific places such as the wall, mitochondria or ribosomes.)
- The nature of the regulatory systems to which it is subject.
- The nature of the cells and tissues that contain the enzyme and how much they contain.

Gradually, answers, or at least models for finding answers, to some of these questions are taking a little more definite shape.

Dr. Gordon Tomkins of the National Institutes of Health in Bethesda, Md., has been using lines of malignant rat liver tissue (hepatoma cells) as a model system for looking at the activity of specific enzymes.

Another approach is to use inbred strains of mice of known and controllable genetic makeup. That way mutation can be identified and used as a tool or distinguishing marker—on the well-proved principle that errors in nature provide insight into normal activity.

From such studies of inbred mice, Dr. Roger Ganschow, a former student of Dr. Paigen, now at the Institute for Developmental Research in Cincinnati, reports a start: The determination of two distinct genetic factors controlling the enzyme catalase in liver. Catalase may be a fossil enzyme. Its only known function is to break down hydrogen peroxide. It was chosen for study because differences in its level and activity were spotted in three inbred mutant strains of mice, thus providing a measure of comparison.

Analysis of variations in catalase levels and in the speeds at which the enzyme catalyzed biochemical reactions revealed that two distinct gene mutations were operating, one controlling levels, the other activity. "The results of this study are particularly significant," Dr. Ganschow says, "in that they document the genetic control of the amount of a specific enzyme in higher organisms."

From investigations of another enzyme, glucuronidase, in inbred mice, Drs. Paigen and Ganschow postulate the existence of several distinct classes of genes.

One class, for which there is ample evidence, is composed of structural genes, those that determine the amino acid sequence and three-dimensional shape of enzymes.

A second class, the researchers propose, is of regulatory genes, which specify the nature of the systems to which enzymes respond and the rate of enzyme synthesis. The quantities of enzymes in cells vary according to physiological demands, and there appear to be three ways in which these levels are determined in higher organisms:

- The first and simplest explanation, once thought to be the single cause of inborn errors of metabolism, is that a defective structural gene fails to order up an enzyme which, therefore, is not present at all.
- A second explanation lies in the regulation of enzyme synthesis: Genetic factors tell a gene to make and stop making a given enzyme.
- The third system regulates the rate at which enzymes, once synthesized, are degraded. Evidence of the existence of this third control system is only now becoming convincing. It is dependent on mammalian studies because enzyme degradation does not occur in bacteria, which discard excess enzymes through a simple dilution process.

Still another class of genes may be temporal genes, elements that activate and deactivate the structural genes,

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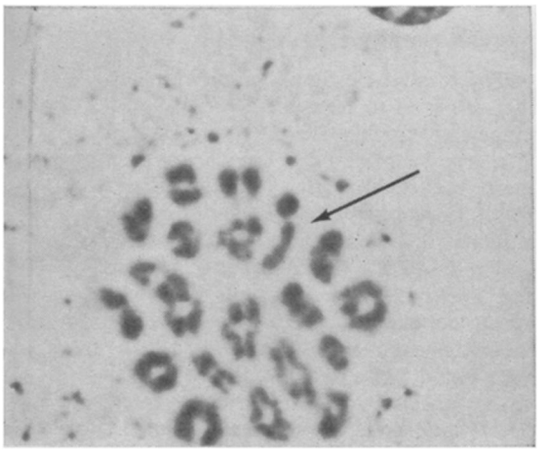
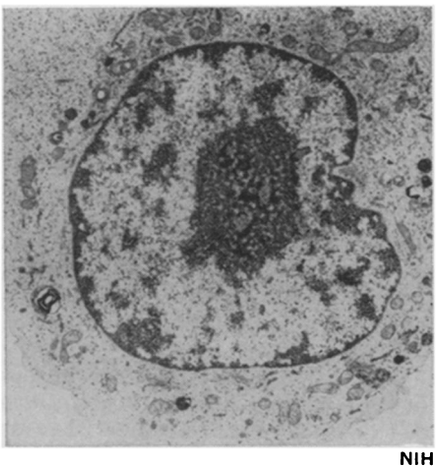
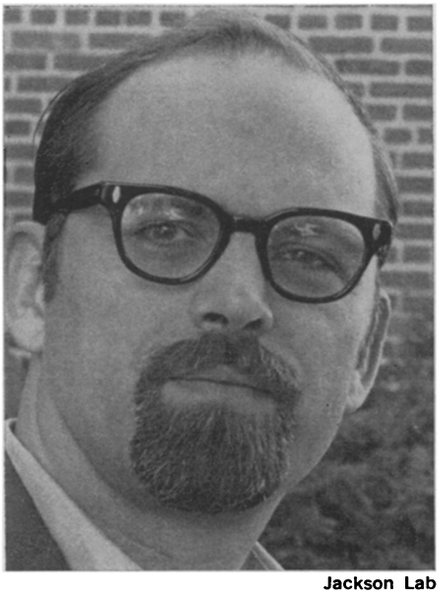


X chromosome: Site of glycogen gene.



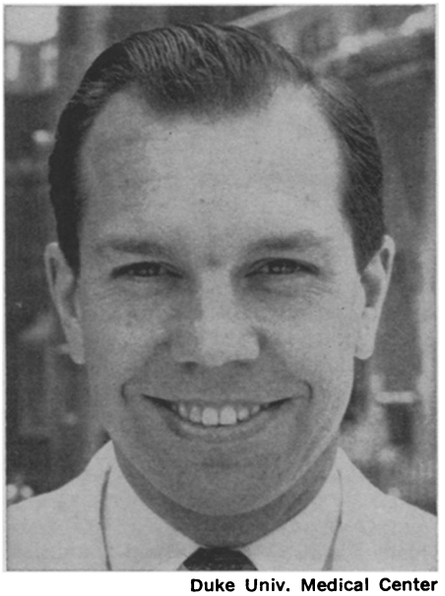
NIH

Rat hepatoma: Enzyme study focus.



Jackson Lab

Ganschow: Genetic catalase control.



Duke Univ. Medical Center

Wyngaarden: "More of everything."

thereby controlling the times at which a particular enzyme is synthesized and accumulated within the cell and thus the times at which levels are high or low.

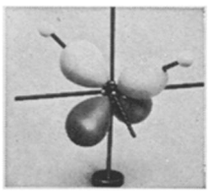
Further, Drs. Paigen and Ganschow suggest, something other than the structure of the enzyme controls where it is located within the cell. "A distinct class of genes may exist which is responsible for the integration of enzymes into subcellular organelles." In mammalian systems, enzymes must be located at the right place in order to function, and the genes that control this may represent a fourth class: architectural genes.

In another report to the symposium concerning studies of glycogen in skeletal muscles (glycogen breakdown is essential for muscle activity), Dr. John B. Lyon of Emory University announced, for the first time, that some of the genetic elements controlling levels of glycogen in muscle tissue at rest are located on the X chromosome.

Specifically, the enzyme phosphorylase kinase, he says, is one of the controlling factors—it may be the major factor—in determining the amount of glycogen; the structural genes that code for this enzyme were identified from research with inbred mouse strains in which the parent consistently has a higher level of muscle glycogen than the offspring.

While stating that this bit of specific information has no immediate usefulness to man—though it could if he learned to manipulate genes—it provides valuable insight to the genetic control systems involved in glycogen activity and could be a model for other work. At present, the chromosomal location of specific genes for a specific enzyme is known to geneticists in only a very few cases.

Although understanding of control or regulatory systems and the genetic factors involved at this point are scanty and, in many cases, imprecise, researchers predicted at the Bar Harbor meeting that progress in the next decade will be as rapid and thorough as was elucidation of the genetic structure and code in the last decade. ◇



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