the hypothalamus by L. Krulich and McCann in 1968. Guillemin and his colleagues determined the structure of GIF to be a tetradecapeptide in 1973 and named it somatostatin. There also is a growth hormone releasing factor (GRF) in the hypothalamus, first reported by R. Deuben and Meites in 1963–64, but its structure has not been determined. Somatostatin inhibits the ability of TRH to release thyrotropin, and surprisingly enough, to inhibit glucagon and insulin secretion by the pancreas, and gastrin and HCl secretion by the stomach. There is evidence that somatostatin is also produced in the pancreas and gastrointestinal tract. There is great interest in the possibility that somatostatin may be useful for treating diabetes and peptic ulcers as well as some growth disorders.

Guillemin was born in 1924 in Dijon, France. He earned the M.D. degree and served in the French Resistance during the German occupation in World War II. In 1948, after hearing a lecture by Hans Selye on stress, he asked Selye whether he could work in his laboratory. Selye agreed and Guillemin went to Montreal in 1948 and there he collaborated with Claud Fortier, who is now at Laval University in Quebec City, on control of ACTH release. In Selye's laboratory, Guillemin learned the fundamentals of experimental endocrinology. After receiving the Ph.D. degree in 1952, he accepted a position in the Department of Physiology at Baylor University Medical School, where he remained for almost 20 years and did the work that culminated in the isolation and structural characterization of TRH.

For a period of 3 years, from 1960 to 1963, Guillemin served as Associate Director of the Laboratory for Experimental Endocrinology at the College de France under the chairmanship of Robert Courrier, commuting between Paris and Houston. While in France he managed to collect several million fragments of sheep hypothalami and published papers in French and English journals dealing with work on TRF and other hypothalamic factors. The principal chemist who collaborated with Guillemin at Baylor was Roger Burgus, who has remained with him to the present time. Guillemin left Baylor in 1972 for the Salk Institute at La Jolla, California, where he is now associate director. He now lives with his wife and children in a home filled with a large collection of artifacts from Mexico and other Latin American countries, and is known as a connoisseur of wines and good food.

Schally was born in Wilno, Poland, in 1926. He and his family fled from Poland to England in 1939. Schally received a Bachelor's degree from the University of London and obtained his first research experience at the prestigious National Institute for Medical Research in Mill Hill, London, between 1949 and 1952. From there he went to McGill University in Montreal, where he earned a Ph.D. degree in biochemistry with Murray Saffran working on the extraction of CRF from the hypothalamus. After obtaining his degree in 1957, Schally moved to Baylor University in Houston to collaborate with Guillemin on the chemical identification of CRF. After 5 years he left to work independently at the Veterans Administration Hospital in New Orleans, and became a Senior Medical Investigator there in 1973. He has at the same time been on the staff of the Department of Medicine at Tulane University School of Medicine since 1962 and is now a professor.

Among the most prominent collaborators of Schally in New Orleans have been Akira Arimura, Abba Kastin, and Cyril Bowers of Tulane University School of Medicine and the Veterans Administration Hospital. Schally is a person of ambition and dedication, and has set an example for long and hard work in his laboratory that would be difficult to match. He and his colleagues have published more than 850 papers since 1962, and he has received many honors prior to the announcement of the Nobel Prize. Proficient in Spanish and Portuguese, Schally is a popular lecturer in Latin America and Spain. His wife is a physician from Brazil who has collaborated with him in clinical testing of hypothalamic hormones.

Finally, it is regrettable that there is no provision for awarding Nobel Prizes posthumously, to recently deceased, outstanding investigators, such as Berson and Harris, who have contributed greatly to an area recognized by the Nobel Committee. Possibly in such cases a medal or certificate could be presented to the institute in which they worked, which would be forever cherished by their families, colleagues, friends, and benefactors.

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Protein Degradation: Putting the Research Together

For many years, biologists have studied how proteins are synthesized and how cells control which proteins are made. The other side of the coin, however, is the breakdown of proteins—a subject whose importance is only slowly coming to be appreciated. Within the past few years, researchers have begun to realize that the regulation of protein breakdown in cells has important implications for problems in genetics, cell biology, endocrinology, and clinical medicine. They are now laying the foundation for studies of how and why proteins are degraded. Of particular interest are discoveries at several laboratories that suggest there may be more than one way to control the breakdown of proteins.

Nearly all proteins are broken down and resynthesized many times within the life of a cell. The average rates at which a cell's proteins are degraded, however, vary with physiological conditions. And different proteins last for vastly different lengths of time before they are destroyed. Some are degraded after minutes, some after hours, and some after days. Evidence is accumulating that cellular controls of average breakdown rates and of the rates at which individual proteins are degraded are both biologically and clinically important.

Since 1951, it has been known that protein degradation is tied to growth control in bacteria. When *Escherichia coli* cells are rapidly growing, they degrade proteins very slowly. When the cells are starved for essential nutrients, their growth nearly ceases and their rates of protein degradation increase severalfold. Moreover, it seems that bacteria use the same signals to cease their growth and to increase their rates of protein degradation. Now it seems likely that correlations between rates of growth and protein degradation are not limited to bacteria. Within the past few years, a number of investigators have found that changes in average breakdown rates are a crucial part of growth control in mammalian cells, tissues, and organs.

Michael Warburton and Brian Poole of Rockefeller University recently reported that there is a high inverse correlation

between the rates that proteins are degraded in cultured fibroblasts and the rates that the cells replicate their DNA in preparation for cell division. So-called growth factors in serum decrease protein degradation at the same time as they stimulate growth. Although there is some evidence that this correlation may not hold for other kinds of cells, Warburton and Poole say they are "forced to conclude that these two cellular processes are tied together by some unknown cellular regulatory mechanisms."

Alfred Goldberg and his associates at Harvard University have studied the links between protein breakdown and the growth and atrophy of skeletal muscle. When a muscle is exercised, protein synthesis increases and protein breakdown decreases. When a muscle atrophies as a consequence of disuse, denervation, starvation, diabetes, or cortisone, protein synthesis decreases and breakdown increases. Recently, Goldberg and J. Fred Dice, who is now at the University of California in Santa Cruz, obtained further evidence in support of an earlier hypothesis that the muscle atrophy found in muscular dystrophy apparently results from an increase in the average rate at which proteins are degraded. They find that muscles from mice with this genetically based disorder synthesize proteins at normal or even greater than normal rates. But the dystrophic muscles have greatly increased concentrations of protein-degrading enzymes and destroy proteins faster than they are made.

Peter Libby of Harvard Medical School and Goldberg now find that a drug called leupeptin that inhibits protein degradation prevents isolated dystrophic muscle cells of mice from wasting away. Alfred Stracher of Downstate Medical Center of the State University of New York reports that when dystrophic chickens are given this drug, their muscles get larger.

Among the organs whose growth rates have been shown to be affected by protein degradation, the liver, in particular, is notable. For example, Oscar Scornik and his associates at Dartmouth Medical School showed that the liver growth occurring after an animal's liver is partially destroyed results primarily from a decreased rate of protein breakdown.

Glenn Mortimore and his colleagues at the Milton S. Hershey Medical Center of the Pennsylvania State University are concentrating on how the liver controls its average rates of protein degradation. Mortimore points out that the liver is the prime regulator of free amino acids in the body. Between meals, the liver breaks down its own proteins and releases their constituent amino acids in order to keep the body's supply of amino acids constant. Mortimore's group finds that when fluids containing amino acids are circulated through isolated rat livers, the rate at which the livers destroy their own proteins decreases. In addition, insulin, which is secreted after meals and which promotes protein synthesis, inhibits protein breakdown in rat liver. On the other hand, they report that glucagon, a hormone with effects opposite those of insulin, promotes protein breakdown in the liver. Others, including Howard Morgan and Leonard Jefferson at the Hershey Medical Center, have found that insulin and amino acids affect protein breakdown in a wide variety of tissues and organs, including the heart and skeletal muscles.

The regulation of the rates at which individual proteins are degraded seems to be important to cellular physiology as well as cellular growth. Robert Schimke and his associates at Stanford University first predicted, nearly a decade ago, that proteins whose concentrations must fluctuate in order to regulate metabolic processes might have short half-lives. More recently, Goldberg and Ann St. John, who is now at Rutgers University, report that there is a relation between the rates that various enzymes are destroyed in the rat liver and the enzymes' positions in biochemical pathways. Those enzymes, called rate-limiting enzymes, that play crucial roles in regulating the flow of substrates through metabolic pathways and whose concentrations fluctuate with physiological conditions are degraded in a matter of minutes or hours. Other enzymes are degraded after much longer periods of time, typically several days.

Degradation of Abnormal Proteins

A number of researchers have found that cells can recognize abnormal proteins and degrade them rapidly. This phenomenon occurs in bacteria as well as in higher organisms. Goldberg and his associates and, independently, Martin Pine of Roswell Park Memorial Institute showed that when bacteria are supplied with analogs of amino acids which they incorporate into proteins, the proteins are quickly degraded. This rapid degradation also occurs when the bacterial cells make mistakes while synthesizing proteins or when, because of nonsense mutations, the protein chains are prematurely terminated. Investigators at a number of laboratories have shown that animal cells behave similarly.

A few years ago, several researchers reported results suggesting that the rapid degradation of abnormal proteins seems to be important in many human diseases. For example, people with genetic disorders that cause them to produce aberrant hemoglobins seem to degrade these proteins very quickly. This is believed to occur among people with so-called unstable hemoglobinopathies, B thalassemia, and perhaps even sickle-cell anemia.

Not only do cells recognize abnormal proteins, but they also recognize protein chains that, for one reason or another, have not been completely assembled into particular structural units. This recognition may also be of clinical importance; Joseph Etlinger, now at Downstate Medical Center, and Goldberg find that it may contribute to anemia caused by iron deficiencies. Hemoglobin is composed of four protein chains and a biochemical complex, known as a heme group, that contains iron. People who lack iron also lack heme groups. Etlinger and Goldberg report that heme groups inhibit the newly synthesized hemoglobin proteins from being degraded in addition to promoting their synthesis.

As yet, no one knows how cells can selectively degrade individual proteins. Some hints, however, have arisen from studies correlating various characteristics of proteins with their rates of degradation. Schimke and others have found that, on the average, larger proteins are degraded more rapidly than smaller ones. Dice and Goldberg found that more acidic proteins tend to be degraded more rapidly than neutral or basic ones. Dice and his associates also found that glycoproteins, which are proteins that contain attached sugars, tend to be degraded more rapidly than nonglycoproteins.

In order to understand how intracellular protein degradation is controlled, researchers are studying where and how it occurs. One obvious possible site for protein degradation is in lysosomes—organelles found in cells of higher organisms. Lysosomes contain high concentrations of degradative enzymes and are known to destroy foreign substances that cells engulf by pinocytosis and phagocytosis.

A number of investigators have studied changes that occur in lysosomes when cells are starved for amino acids or are deprived of insulin and thus begin to rapidly degrade proteins. From these studies, they have obtained evidence that lysosomes are a major, if not the only, site where proteins are broken down. Mortimore and his associates, for example, find that when they force fluid

that does not contain insulin or amino acids through isolated rat livers, liver proteins are degraded at increased rates and the liver lysosomes become heavier and grow larger (Fig. 1). When they force liquid containing insulin or amino acids through the livers, these lysosomal changes do not occur and the livers do not speed up their rates of protein degradation. In addition, the larger and heavier lysosomes of the livers deprived of insulin and amino acids actually contain more proteins than the lysosomes of livers supplied with these substances. According to Mortimore, their studies directly indicate that the lysosomes take up cellular proteins when livers increase their rates of protein breakdown.

Scornik also believes the lysosomes are the only sites where proteins are degraded. He bases this belief on experiments by himself and his colleagues on protein breakdown in rat liver. When the livers are actively growing, the average rates of protein breakdown decrease significantly. Scornik and his associates then asked if the rates of abnormal protein degradation also decrease. They found that, although such rates are still much greater than the average rate of protein breakdown in growing livers, the abnormal proteins are degraded significantly more slowly in growing than in nongrowing livers. The simplest explanation of these results, Scornik says, is to postulate the same mechanism, at least in part, for all protein degradation.

Other evidence that lysosomes are an important site of protein degradation is reported by Goldberg and his associates. George Griffin and Goldberg find that excess amounts of thyroid hormone increase the rates of protein destruction in muscle and liver cells (which may explain in part why people with hyperthyroidism lose weight and body proteins). George De Martino and Goldberg report increased numbers of lysosomal enzymes in cells of organs affected by the excess hormone but not in other cells of the same animal. Others have found that lysosomes increase in number under various conditions in which protein breakdown increases, including muscular dystrophy and muscle atrophy following the cutting of nerves leading to a muscle.

In contrast, however, several investigators have recently begun to question the hypothesis that lysosomes are the sole or major site of protein degradation. One indication that they may not be the major site comes from studies by Dice and Carlos Walker, who asked whether the accelerated rates of protein breakdown associated with poor nutritional

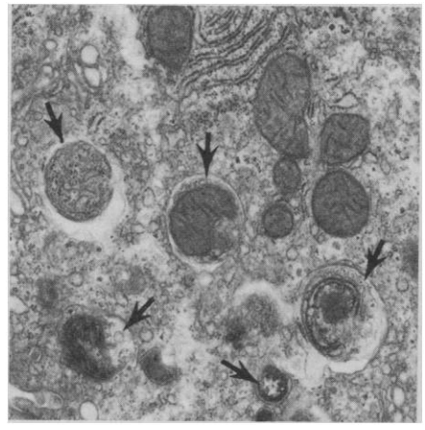

Fig. 1. Electron micrograph of a portion of a liver cell that has been deprived of amino acids. Arrows indicate enlarged lysosomes. [Source: Glenn Mortimore, Pennsylvania State University]

conditions resulting from diabetes or starvation are due to increased rates of normal processes controlling protein degradation or to fundamentally different processes. They initiated these studies because most evidence about lysosomal degradation was obtained from studies of starved or diabetic rats.

Dice and Walker report that, in livers and muscles of starving or diabetic rats, large proteins are not degraded more rapidly than small ones, acidic proteins are not degraded more rapidly than neutral or basic ones, and glycoproteins are not degraded more rapidly than neutral or basic ones. Since this contradicts what is known about normal protein degradation in plant and animal cells, Dice and Walker suggest that proteins are degraded by abnormal mechanisms when animals are starved or diabetic. They suggest that the evidence that lysosomes are the major sites of normal protein degradation may have to be reexamined.

Brian Poole and his associates and, independently, F. John Ballard of the Commonwealth Scientific and Industrial Research Organisation (CSIRO) in Adelaide, Australia, report other evidence that a substantial amount of protein may be degraded outside the lysosomes. Poole and his colleagues exposed mouse macrophages (scavenger cells) to various substances that inhibit lysosomal enzymes and found that these substances greatly decrease the degradation of extracellular substances engulfed by the cells. In contrast, the substances did not seem to affect the rate that the cells degrade their own intracellular proteins, unless the cells are exposed to poor nutritional conditions. The Rockefeller group reports similar results with rat fibroblasts. Ballard has found with liver cells, that such inhibitors affect only the degradation of the most stable cell proteins. Poole and his colleagues conclude, however, that although they have evidence for a nonlysosomal mechanism of protein breakdown, "since we have no idea where or what this 'other' proteolytic mechanism may be, considerable caution is necessary in the interpretation of such results."

Direct evidence of a nonlysosomal system for protein breakdown has been reported by Etlinger and Goldberg, who studied the degradation of abnormal hemoglobins by cell-free extracts of immature red blood cells from rabbits. The abnormal hemoglobins were made when intact red blood cells were supplied with an amino acid analog, which the cells subsequently incorporated into hemoglobin molecules. The resulting abnormal proteins have half-lives of 15 minutes in intact cells. Normal hemoglobins, Goldberg points out, last the lifetime of the red blood cell—about 110 days.

Etlinger and Goldberg found that the cell-free extracts of the red blood cells, which do not contain lysosomes, rapidly degrade the abnormal hemoglobins without affecting the normal proteins within the same cells. Moreover, the extracts degrade several other abnormal polypeptides at rates similar to those in intact cells. The degradation of abnormal hemoglobins by these extracts requires an energy source—adenosine triphosphate (ATP). Bacteria, Goldberg points out, are known to have a similar ATP-requiring system to degrade abnormal proteins. This system may be used to degrade some normal bacterial proteins as well. Recently, Jeffrey Roberts at Cornell University and his associates reported that when the bacterial virus lambda is induced to replicate itself, the bacteria degrade a specific viral repressor protein. This degradation requires ATP.

Goldberg emphasizes that in both bacteria and red blood cells, the degraded abnormal proteins form large aggregates, which show up as dense granules in electron micrographs. These granules may be important in various human diseases. For example, they show up in thalassemias, where they are known as Heinz bodies.

The controversy over the site of protein breakdown notwithstanding, most investigators now believe they are making real progress toward understanding and appreciating the control and functions of protein degradation in cells. Although protein synthesis still commands most biologists' attention, studies of protein breakdown are finally coming into their own.—GINA BARI KOLATA