trations of glucagon would be the liver-mediated release into the bloodstream of inappropriately high concentrations of glucose, thereby producing a persistent hyperglycemia.

Glucagon also appears to regulate the oxidation of fatty acids in the liver and thus may be involved in the most severe short-term effect of diabetes—ketoacidosis. Ketoacidosis is the increased production of so-called ketone bodies, such as β-hydroxybutyric acid; release of these ketone bodies into the blood lowers its *p*H, inducing coma and, if the condition is not corrected, death. K. G. M. M. Alberti and his associates at the University of Southampton in England have shown that there is a definite correlation between the concentrations of glucagon and ketone bodies in patients with ketoacidosis.

Gerich and his associates have shown that withdrawal of insulin from insulin-dependent diabetics produces increases in the concentrations of many compounds associated with ketoacidosis—such as β-hydroxybutyric acid, free fatty acids, and glycerol—that can be correlated with the increase in the concentration of glucagon in the blood. At the University of Texas Southwestern Medical School, J. Denis McGarry and his associates have demonstrated that administration of glucagon to rats in the absence of food alters the metabolism of the rat livers so that the livers produce products characteristic of ketoacidosis. Ketoacidosis itself does not appear, however, because of the counterbalancing effects of insulin stimulated by the glucagon.

Conventional therapy for ketoacidosis is the administration of insulin. It now appears that the primary effect of the insulin may be suppression of the release of glucagon. Since insulin can mediate only a limited reduction in the concentration of glucagon, it seems likely that a more effective therapy would be administration of somatostatin. Gerich has recently demonstrated, in fact, that infusion of somatostatin prevents the development of ketoacidosis in insulin-dependent diabetics deprived of insulin.

Despite the remarkable preliminary successes with somatostatin in the therapy of diabetes, a great many problems must be resolved before there can be any substantial use of the new hormone. Perhaps the most difficult problem now is that somatostatin can be given only by infusion because its effects are so short-lived (see box). Investigators are now searching for analogs of the hormone that will persist longer in the bloodstream.

A severe problem for the long term is that somatostatin therapy might be inappropriate for youthful diabetics because it also inhibits the release of growth hormone. Many investigators are confident, however, that the development of somatostatin analogs will provide agents that are more selective in their action. It is possible also that somatostatin could be given to such individuals only in conjunction with meals; the agent would thus not interfere with growth hormone, which is released primarily during sleep.

A perhaps less important problem is that very few investigators can explore therapy in humans with somatostatin. Only Roger Guillemin has an Investigational New Drug permit from the Food and Drug Administration for use of somatostatin in humans. The practical consequence is that experimental therapy of humans with the hormone can be conducted only by the small group of investigators who work with him or by investigators in certain foreign countries.

And finally, many investigators have been concerned by reports by Donna J. Koerker of the University of Washington Medical School, who has suggested the possibility of an association between somatostatin administration and the deaths of several baboons. Koerker observed an unusual frequency of pulmonary and hepatic hemorrhaging in baboons that had been given frequent injections of the hormone. Subsequent experiments showed that somatostatin exerts a transient effect on the aggregation of platelets (which are responsible for clotting) comparable to that of aspirin. Koerker, furthermore, suggests that the effect is probably dose-related. The doses of somatostatin given to the baboons were about ten times as great as the highest dosages used by Gerich in humans, and Gerich has not been able to demonstrate the effect on platelets at the lower doses. Nonetheless, the possibility remains that arbitrary and empiric doses of somatostatin may affect nonendocrine cells.

Thus many years may pass before the results of this research will be used in human therapy. But it seems safe to predict that these developments will eventually result in a sharply improved therapy of diabetes and a reduction in the side effects that accompany the disease.

—THOMAS H. MAUGH II

Foundations of Mathematics: Ties to Infinite Games

Game theory has become increasingly important to the study of the foundations of mathematics. Strategies for winning one group of games, in particular, have been subject to intensive investigation by logicians. These games, as the logicians soon realized, are intimately connected to the structure of a collection of sets that are crucial to almost all theories in pure and applied mathematics. Exactly how the games and those sets are related was recently demonstrated by a proof that represents the first result in ordinary mathematics that requires the full power of set theory.

The games that have come to be so important to mathematicians were first introduced in 1953 by David Gale and F. M. Stewart, who were then at Brown University. Gale and Stewart analyzed these games in order to better understand other games rather than to study the foundations of mathematics. However, they discovered a connection between strategies necessary for winning these games and one of the axioms of set theory. This connection caught the attention of logicians who realized that it could lead to major results about the structure of sets.

The games introduced by Gale and Stewart are infinite games: that is, each of these games does not end until the players have made an infinite number of moves. Such a game is played by two participants who alternately pick the numbers 0 or 1 and record their choices at each turn. The game ends when the players have recorded an infinite sequence of 0's and 1's. The first player wins the game if this infinite sequence belongs to a collection of infinite sequences, called the payoff set, that was chosen before the game began. The second player wins if the infinite sequence does not belong to the payoff set. For example, the payoff set could consist of all those sequences produced when a 1 is recorded for the 1st move, 5th move, 7th move, 11th move, and so on. The first player could win a game that has this payoff set since he chooses all of the odd-numbered terms of the infinite sequence. Gale and Stewart then asked: Is every possible payoff set associated with a winning strategy for player 1 or player 2?

John von Neumann and Oscar Morgenstern had shown previously, in the 1930's, that finite versions of the games considered by Gale and Stewart—that is, games that end when each player has taken only a finite number of turns—always have winning strategies for one player or the other. Gale and Stewart found, however, that if the game is infinite, there will always be payoff sets for which there are no winning strategies, so long as one assumes that the axiom of choice, on which much of modern mathematics is based, is true. This result caused many investigators to wonder if payoff sets that are associated with winning strategies might be special sets. For example, they could have particular sizes or structures. Mathematicians tried to discover the consequences of assuming that a set is associated with a winning strategy and, at the same time, tried to identify those sets that are associated with winning strategies.

Jan Mycielski and H. Steinhaus, who were then at Wroclaw University in Poland, began the study of payoff sets associated with winning strategies when they named those sets "determined" and investigated the consequences of assuming that every set is determined. This turned out to be such a strong assumption that many mathematical theories based on the axiom of choice could also be derived from this assumption, which Mycielski and Steinhaus called the axiom of determinacy. In addition, they showed that if the axiom of choice were replaced by the axiom of determinacy, many undesirable phenomena would disappear. For example, not every set of numbers has a well-defined size if the axiom of choice is assumed. If the axiom of determinacy is assumed, each such set does have a well-defined size. They went so far as to suggest that perhaps the axiom of choice should be replaced by the axiom of determinacy.

Mathematicians were reluctant to give up the axiom of choice, which they regard as an intuitively reasonable and a useful axiom, in favor of an axiom of determinacy. However, when they retain the axiom of choice, they must live with the fact that some sets will not be determined. The question is, which sets?

A natural guess would be that the sets that are not determined are among the sets that have never been described or defined, according to Yiannis Moschovakis of the University of California at Los Angeles. It is known that most sets cannot be explicitly described, and no one has succeeded in describing a specific set and proving it undetermined.

In many instances, mathematicians have been unable to show that arbitrary members of the collection of all sets have certain desirable properties. However, if they restrict themselves to sets that can be explicitly defined, they can often analyze the properties of those sets. For example, they can show that any set in the collection of simply definable sets—that is, sets with definitions that are sufficiently simple, in a certain technical sense—has a size that can be measured, whereas any set from the collection of all possible sets may not have a measurable size. Since the assumption that a set is determined can be used to infer many useful consequences about its structure some researchers chose to assume, as a working hypothesis, that every set they could explicitly define is determined.

The hypothesis that definable sets are determined turned out to be very useful in studying the structure of sets. For example, William Wadge, a student of John Addison, at the University of California at Berkeley, used this hypothesis to derive a way to classify and describe the structure of the Borel sets. These sets, which are definable, are part of the backbone of theories that underlie large areas of mathematics, such as analysis, much of applied mathematics, and probability theory. The notion of the integral of calculus, for example, is generalized by means of a theory that involves functions that behave well on Borel sets. And probabilities are defined on all the Borel sets.

Another class of sets that are important to many kinds of mathematical theories is the projective sets. Since these sets can also be defined, Addison, along with Donald A. Martin of Rockefeller University and Moschovakis, assumed they were determined. They then found that they could derive a powerful result about the construction and structure of these sets. Since that time almost the entire theory of the structure of projective sets has been worked out from the hypothesis that these sets are determined.

Borel Sets Are Determined

Since the hypothesis that definable sets are determined was leading to such desirable results, many investigators hoped to demonstrate that some of the major classes of definable sets actually are determined. They focused their attention on the Borel sets, in part because these sets are of such great importance to theories in pure and applied mathematics. Deciding whether the Borel sets are determined was an outstanding open problem until this year when, at the meeting of the American Mathematical Society, held on 21 to 27 January 1975 in Washington, D.C., Martin reported his proof that they are indeed determined. His result has been received with a great deal of enthusiasm in part because the difficulty of this problem was well established by work that preceded his proof.

Following Gale and Stewart, who posed the problem, many researchers concentrated on deciding whether the Borel sets are determined. For example, Philip Wolfe of the I.B.M. Thomas J. Watson Research Center showed that certain special Borel sets are determined but could not obtain this result for all of the Borel sets. This work was recently extended by J. Paris of the University of Manchester in England who showed that still more of the Borel sets are determined.

The next advance in showing that all the Borel sets are determined came when Martin found that if he added another axiom—the axiom of the first measurable cardinal—to the usual axioms of set theory, he could show that both Borel sets and a few simple projective sets are determined. However, use of the axiom of the first measurable cardinal, which asserts the existence of certain very large sets, is controversial because, when it is added to the usual axioms of set theory, it greatly affects what can be proved from those axioms. Thus most investigators would prefer not to use this axiom to prove the Borel sets are determined.

Recently, Harvey Friedman of the State University of New York at Buffalo showed that no ordinary methods of proof would suffice to show that the Borel sets are determined. He demonstrated that the full power of the axioms of set theory would be needed for this result by showing that the replacement axiom, which is one of the usual axioms of set theory but one that is rarely used in practice, must be used to prove the Borel sets are determined. According to Robert Solovay of the I.B.M. Thomas J. Watson Research Center, very few proofs in mathematics even look as though they use the full power of the axioms of set theory. The entire field of algebraic topology, he points out, is based on only a weak form of those axioms. From Friedman's work, then, it became clear that finding a proof that the Borel sets are determined would be difficult.

Martin's proof that the Borel sets are determined, which uses the full power of the axioms of set theory, is hailed not only because it is esthetically pleasing but because it is the solution to a major open question that relates to many areas of mathematics. And although results filter slowly through the mathematical community, some who know of Martin's proof are confident that it will be important in many areas of mathematics since it provides a way to derive a concrete description of the asbtract Borel sets in terms of strategies for winning an infinite game.

—Gina Bari Kolata