One approach to this problem, which was used in both laboratories, depends on the formation of "caps" when cells are exposed to antibodies against membrane components. The antibodies, usually labeled with a fluorescent molecule, bind to antigens on the membrane. The antibody-antigen complexes coalesce to form caps on the cell surface. When cells were exposed simultaneously to antibodies against β_2-microglobulin, labeled with one fluorescent molecule, and antibodies to histocompatibility antigens, labeled with a different one, the caps that formed contained both antibodies.

The role of β_2-microglobulin and, for that matter, of the histocompatibility antigens is uncertain. Because of the resemblance of β_2-microglobulin to segments of the IgG molecule and its location on lymphocyte surfaces, some investigators have hypothesized that it functions in such aspects of immune responses as recognition of antigens and interactions between T and B lymphocytes.

Poulik, with Marilyn Bach, of the University of Wisconsin, Madison, found that antibodies against β_2-microglobulin can block some in vitro responses of lymphocytes (probably T lymphocytes). The responses are thought to depend on recognition of antigens by receptors on the cell surface. Poulik warns that such data must be interpreted with caution. In other assays, the antibodies did not interfere with lymphocyte activity. The identity of T cell receptors for antigens is now a subject of considerable controversy.

A current hypothesis about the function of histocompatibility antigens involves the possibility that they may be involved in genetic control of immune responses. Most of the immune response genes—those that control an animal's capacity to respond to a given antigen—are located in the same chromosomal segments as the genes that specify histocompatibility antigens. Some immunologists think that the immune response genes and the histocompatibility genes may be identical. They have also speculated that the products of the immune response genes are T cell receptors that function in antigen recognition and cooperation between T and B cells.

Thus, β_2-microglobulin is associated with the histocompatibility antigens. Its structure implies both a common evolutionary origin for immunoglobulins and histocompatibility antigens and also an immunological function for the molecule. Since β_2-microglobulin and the histocompatibility antigens are not restricted to cells of the immune system, they may have additional, although still unknown, functions.

Edelman and J. A. Gally, who is at Meharry Medical School, Nashville, Tennessee, have suggested that the immune system, with its specialized function, has evolved from the more primitive, generalized system of the histocompatibility antigens. If the larger histocompatibility component has an amino acid sequence homologous to that of the immunoglobulins, this will lend additional support to their hypothesis.

The chromosomal location of the gene for β_2-microglobulin is not yet known, but this critical experiment is undoubtedly being vigorously pursued. If the gene is found in the same chromosomal region as the immune response and histocompatibility genes, β_2-microglobulin may be an important clue to the solution of a number of major problems in immunology.

—JEAN L. MARX

Riemann Hypotheses: Elusive Zeros of the Zeta Functions

For more than a century, mathematicians have tried to resolve the classical Riemann "hypothesis"—a conjecture that, if true, would provide information about the distribution of the prime numbers. Attempts to solve this problem have led to generalizations of it and to the advancement of conjectures that resemble, but are distinct from, the original one. Now, although the classical Riemann hypothesis remains unresolved, a class of similar conjectures has been proved true by P. Deligne of Institut des Hautes Etudes Scientifiques in Paris in work that draws on 50 years of research by others in several fields of mathematics. This proof and recent progress toward solutions to problems that are related to the classical Riemann hypothesis have led many to believe that a resolution of the classical conjecture may be forthcoming during this century.

Since all natural numbers which are not primes can be broken down into unique products of primes, describing the distribution of primes is a fundamental problem in number theory. Describing how prime numbers occur in the number system is related to describing the behavior of a function [the Riemann zeta function, $\zeta(s)$*] which is defined for complex numbers. The function is zero when it is evaluated at certain points that lie in the critical strip, an infinite vertical strip in the complex plane (Fig. 1). Answers to many of the outstanding problems in number theory hinge on the location of those points in the critical strip.

Riemann conjectured that all zeros of the zeta function [solutions to the equation $\zeta(s) = 0$] which are in the critical strip lie on the vertical line that divides that strip in half (the critical line). This conjecture is known as the classical Riemann hypothesis. If it is true, knowledge of how the primes occur will be greatly extended. It has long been known that a function, $\mathrm{Li}(x)$,† provides a good approximation to the number of primes in the interval from 0 to x. If the classical Riemann hypothesis is correct, then the error term associated with that approximation would be small. In addition, information on the size of the gaps between the primes could be obtained.

The classical Riemann hypothesis resembles other kinds of conjectures known as the Riemann "hypotheses" for algebraic varieties. Like the classical hypothesis, these concern the location of zeros of zeta functions. The zeta functions associated with these analogous proposals have properties similar to those of the zeta function associated with classical hypothesis. However, they are more easily analyzed than the classical function. Nonetheless, a new field of mathematics had to be developed before Deligne could finally resolve the most general of these hypotheses.

Algebraic varieties are defined by polynomial equations (such as $x^3 + y^2 + 1 = 0$). They are associated with zeta functions which can be described

* $\zeta(s) = \sum_{n=1}^{\infty} n^{-s}$ for the real part of s greater than 1 and is analytically continued for all complex $s \neq 1$.

† $\mathrm{Li}(x) = \int_2^x \frac{dy}{\ln y}$

by regarding certain points on the varieties as generalizations of primes. These points define the variety just as the primes define the natural numbers. In the same way as the Riemann zeta function provides information about the number of primes less than or equal to some number x, the zeta functions of algebraic varieties provide information about the number of their solutions. An estimate of the number of solutions to these equations is equivalent to the statement that the zeros of their corresponding zeta functions lie on certain lines.

The Riemann hypothesis for one-dimensional varieties (algebraic curves) was proved in 1940 by A. Weil of the Institute for Advanced Study in Princeton. Weil conjectured in 1949 that this hypothesis could be extended to varieties of dimension greater than 1.

Deligne's recent work in proving Weil's conjectures about the Riemann hypothesis for algebraic varieties and results in the field of algebraic geometry (a branch of mathematics central to Deligne's proof) have significant applications. For example, Deligne has now used his results to prove a conjecture made by the Indian mathematician S. Ramanujan that provides information about the Dedekind delta function. A problem involving this function is important to physicists and applied mathematicians as well as to number theorists. Deligne reduced the problem to one about a Riemann hypothesis for a certain algebraic variety. Unfortunately, Deligne's work has not provided a means to resolve the classical Riemann hypothesis. Progress toward a solution to this problem is slow and indirect.

An unsuccessful straightforward attempt to disprove the classical Riemann hypothesis was made by L. Schoenfeld of the State University of New York at Buffalo together with J. B. Rosser and J. M. Yohe of the University of Wisconsin in Madison. This group

Speaking of Science

Mathematical Problems: A Committee to Replace Hilbert

As long as a branch of science offers an abundance of problems, so long is it alive; a lack of problems foreshadows extinction or the cessation of independent development.—DAVID HILBERT

According to Hilbert's criterion, mathematics is very much alive. In fact, many believe that its vitality has increased since Hilbert's time. In 1900 Hilbert, who was one of the most influential mathematicians of the past century, enumerated 23 outstanding problems in mathematics. The subsequent research on those problems led to the development of new fields of mathematics and had a profound influence on the mathematics studied today. Now most of Hilbert's problems have been solved, and contemporary mathematicians are attempting to formulate a new list of problems which, they hope, may prove as important to future mathematical research as Hilbert's list was to research in the past.

The formulation of a new problem list turns out to be a difficult task. Mathematics has changed since Hilbert's day. The body of knowledge has expanded so much that probably no one investigator today has a command over research in as many areas as Hilbert had in 1900. Thus, acknowledging the impossibility of finding a latter-day Hilbert, mathematicians formed a committee, headed by J. Dieudonné of the Faculty of Sciences in Nice, France, to suggest significant problems. The resulting list of problems was discussed at a symposium of the American Mathematical Society held on 13 to 17 May 1974 at the University of Northern Illinois in De Kalb.

A list chosen by a committee could hardly be expected to please everyone, but the consensus at the meeting was that the problems include some of the major questions in modern mathematics. For example, V. Arnold of the University of Moscow asked why many apparently independent classification theorems are all associated with the same set of Coxeter-Dynkin graphs. Such classification theorems include those associated with the platonic solids and with categories of linear spaces and maps. A solution to Arnold's problem would thus unify a group of seemingly diverse concepts. Other problems include solving the classical and generalized Riemann "hypotheses" (see accompanying article) and providing an analytical (rather than statistical) description of turbulence.

The new list has been criticized by P. R. Halmos of Indiana University for omitting some important problems in analysis and by R. Graham of Bell Laboratories in Murray Hill, New Jersey, for omitting problems in combinatorics and computer algorithms. Other criticisms were voiced by several investigators who believe that modern mathematics is so diverse that its important problems cannot be enumerated in a short list. Moreover, many feel that it is nearly impossible to state some of those problems without resorting to technical language that is incomprehensible to those who have not studied certain highly specialized areas of mathematics. Problems for future research, they believe, cannot fulfill one of Hilbert's criteria, that they be clearly stated and easily understood.

However, not all of Hilbert's problems were easily understood by nonspecialists. In addition, Hilbert never intended that his list encompass all the important mathematical problems of his day. He included problems in fields in which he had been active but omitted problems in other fields, such as topology, in which he had not worked. Thus, many believe that comparisons of the problems posed by Dieudonné's committee with those posed by Hilbert should take into account the limitations of Hilbert's problems. As L. Bers of Columbia University points out, a complete list of important problems is nearly impossible to collect for a field as rich and diverse as modern mathematics. Bers quotes Georg Cantor, a mathematician of the past century, who said, "The essence of mathematics is its freedom." Thus, recognizing the near impossibility of prophesying the future of mathematics, Dieudonné's committee is hoping that it, like Hilbert, may popularize a sample of interesting problems.—G.B.K.

used a computer to calculate the first 3.5×10^6 and also the first 41,600 zeros following the 13,400,000th zero of the infinite number of zeros of the Riemann zeta function that lie in the critical strip. If they had found a zero of this function that was not on the critical line, then the classical Riemann hypothesis would be false. However, all of these two groups of zeros were on the critical line, and so the problem remains unresolved.

Schoenfeld and his colleagues are now using these zeros to improve the accuracy of certain inequalities that describe distributions of primes. However, they and others believe that it may be futile to hope to disprove the Riemann hypothesis with computer calculations, even if the hypothesis is false. The distribution of primes is so irregular that many phenomena occur only for primes so large as to be beyond the range of present-day computers.

Even though the primes have been tabulated with computers for numbers up to 10^{10}, at least one known phenomenon is not observable from this list. As I. Richards of the University of Minnesota points out, mathematicians have proved that at some point the graph of the function $\pi(x)$, which is the exact number of primes less than or equal to x, will cross the graph of the function $\mathrm{Li}(x)$, the approximation to $\pi(x)$. However, the calculation of primes for numbers up to 10^{10} provides no clue to where they will cross. For all of these numbers $\pi(x)$ is less than $\mathrm{Li}(x)$. Richards mentions that A. E. Ingham of Kings College, Cambridge, has conjectured that they will first cross for some number x larger than 10^{700}. If this is true, since $\pi(x)$ must be calculated explicitly by counting the number of primes less than or equal to x, the calculation of $\pi\ (10^{700})$ is in practice beyond the range of a computer.

Some results consistent with the classical Riemann hypothesis were recently reported by N. Levinson of the Massachusetts Institute of Technology, who finds that at least one-third of the zeros of the Riemann zeta function which are in the critical strip are on the critical line. Since there are infinitely many zeros of the function in the critical strip, Levinson used the mathematical technique of describing their distribution by counting the number of zeros in a finite portion of the strip and then letting the size of this finite portion increase without bounds.

The classical Riemann hypothesis implies that the gap between two con-

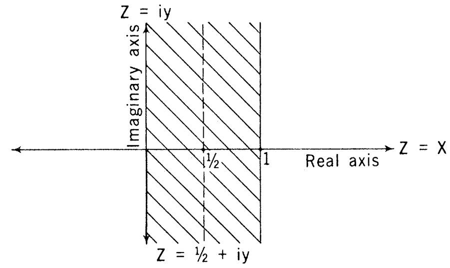

Fig. 1. The critical strip and the critical line. The critical strip is shaded; the critical line is given by the equation $z = \frac{1}{2} + iy$. Each complex number z in the complex plane is a sum of a real number x and an imaginary number iy where $i = (-1)^{1/2}$ and y is a real number.

secutive primes, p_n and p_{n+1}, is at most $p_n^{1/2+\epsilon}$ where ε is an arbitrarily small positive number. This estimate follows from the classical conjecture because information about the overall distribution of primes can be used to estimate the distance between primes. The converse statement, however, is not true, and so results about gaps between primes cannot be used to resolve the classical hypothesis. No one has yet shown that the gap between two consecutive primes, p_n and p_{n+1}, is at most $p_n^{1/2+\epsilon}$, but M. N. Huxley of University College in Cardiff, Wales, has now shown that the gap is at most $p_n^{7/12+\epsilon}$.

Closely associated with the classical Riemann hypothesis is another class of generalized Riemann "hypotheses" which provide more information about primes than does the classical conjecture. Research on these generalized conjectures has led to a result that they are, on the average, correct.

The generalized Riemann hypotheses provide information about the distribution of various classes of primes (such as those, like 41, which end in 1 compared to those, like 43, which end in 3). These results are important to many areas of number theory and are related to problems in other fields of mathematics, such as the study of Fourier series (infinite sums of trigonometric functions). Certain functions that are important to number theorists may be approximated by these infinite sums, and mathematicians often need to calculate the values of finite, but very large, portions of the sums. If the generalized Riemann hypotheses were true, many of the terms in such a finite portion would cancel, and thus its computation would be greatly facilitated.

The classes of primes which are the subjects of the generalized Riemann hypotheses are defined by arithmetic progressions (sequences of the form $an + b$, where a and b are constants and $n = 0,1,2, \ldots$). For example, all primes that end in 7 belong to the progression $10n + 7$. The generalized Riemann hypotheses are equivalent to statements that the primes are uniformly distributed (with a small, explicit error) among all possible arithmetic progressions.

The most spectacular result related to the generalized Riemann hypotheses was obtained by E. Bombieri of the Institute for Advanced Study in Princeton and the University of Pisa in Italy and, independently, by A. I. Vinogradov of the University of Leningrad. Bombieri took the average of the errors in distributions of primes over a large group of arithmetic progressions and showed that this average is exactly as predicted by the generalized Riemann hypotheses. This result is equivalent to a statement about the average distribution of zeros of the Riemann zeta functions in the critical strip.

Although zeta functions were originally studied because they contain information about the distribution of primes, they are currently of interest because they contain topological and geometrical, as well as analytical, information. Bombieri points out that zeta functions are now used to express, in simple ways, many deep theorems. Some mathematicians hope to go still further and develop a theory of so-called Hasse-Weil zeta functions that would unify all of the Riemann hypotheses, including the classical one. These all-encompassing zeta functions have been defined and their properties have been conjectured. However, no one has yet succeeded in verifying these properties for any but a few special cases.

The connection between zeros of zeta functions and so many seemingly unrelated concepts indicates to Bombieri that these zeros must correspond to some delicate mathematical objects. He goes so far as to say that mathematicians don't need a resolution of the classical Riemann hypothesis as much as they need an understanding of the meaning of the zeros of zeta functions. In this way, the development of the theory of zeta functions, which has led to outstanding work in algebraic geometry and topology, may lead to a new understanding of relations among mathematical concepts and may lead, at last, to a resolution of the classical Riemann hypothesis.—GINA BARI KOLATA

Additional Readings

1. L. Goldstein, *Am. Math. Mon.* **80**, 599 (1973).
2. N. Levinson, *Proc. Natl. Acad. Sci. U.S.A.* **71**, 1015 (1974).