second possible contribution to the daily life of an organism, through variable splicing. If the excision of intervening regions and subsequent joining of coding regions can take place in, say, two slightly different patterns, then a single gene could give rise to different messenger RNA's and therefore to two different protein molecules. "We appear to have an example of this with human growth hormone," says John Baxter of the University of California, San Francisco. "One of the intervening sequences in the human growth hormone transcript is processed in two ways, giving two hormone variants. One of them has a molecular weight of 20,000 and growth stimulating properties but does not affect carbohydrate metabolism; the other is 10 percent larger and has both metabolic properties." Variable splicing is clearly a possible fertile source of metabolic nuance.

When molecular biologists talk about their attempts to analyze gene action, it is easy to get the impression that DNA is naked in the nucleus, that all that is important is the sequence of nucleotide bases that make up the DNA strand. DNA is not naked in the nucleus: it is packaged by being coiled around tiny protein spheres, producing the effect of a string of beads. The combination of DNA and protein beads is known as chromatin and is special to nucleated cells. "Chromatin must have a profound effect on the way genes work in these cells," emphasizes O'Malley. The question is, is the effect a passive one arising from the physical constraints of packaging, or does it involve more specific interactions that determine that one gene shall be active in a particular cell while another remains silent?

> "Chromatin must have a profound effect on the way genes work in these cells."

When a cell differentiates, that is, becomes specialized as, for instance, a liver cell, a particular suite of genes pertinent to the cell's future activity is put into a state of readiness. "This involves a different conformation of chromatin," explains O'Malley. "The genes, and a large area around them, are now sensitive to a DNA digesting enzyme." Once a gene receives a signal to start transcribing, its sensitivity to DNA digestion increases still further, especially around the initiation site. This implies that the arrangement of chromatin beads is different—more open—in pregnant and active genes, and some researchers claim that this rearrangement derives from specific interactions between the DNA sequences and the proteins. Others dispute the specificity of interaction. This is an area where the meeting of molecular and cellular biology has yet to yield unequivocal results.

One specific suggestion for DNA/protein interaction in chromatin relates to the structure of the promoter region. Harold Weintraub, of the Fred Hutchinson Cancer Center, Seattle, suggests that packaging in this area aligns functional sequences in important ways. "One turn of the DNA strand round a bead would bring the TATA box and the CAT box right next to each other," he claims. "And another turn would align them with the next upstream region at −150." This comment may display a keen eye for the importance of three-dimensional structure in the interaction of DNA with the RNA polymerase. Or the spacing of these regions may be merely coincidental. It turns out that at least some genes are devoid of protein beads around the promoter region, so that the coiling notion cannot apply in these cases. Currently the alignment of sites on beads is interesting speculation.

Just as DNA does not go naked in the nucleus, so too does RNA find itself clothed in protein molecules during its journey from the site of transcription to the pore in the nuclear membrane through which it exits. This stage of gene expression—termed RNA processing—has more puzzles and fewer firm answers than almost any other.

In outline, the process is this: A complete RNA transcript of the coding and noncoding mosaic is made by RNA polymerase. A small chemical residue, or a cap, is added to the front, $5'$ end, of the transcript. A string of around 200 adenine molecules, the poly(A) tail, is added to the back, $3'$ end, of the transcript. The noncoding regions are cut out. The coding regions are stitched back together in the same order as they appeared in the DNA. And the mature message exits into the cytoplasm where protein synthesis may begin.

Questions relating to RNA processing may be divided into two areas: those relating to the excision of the intervening sequences; and those concerning the interaction of the RNA transcript with other molecules, such as proteins.

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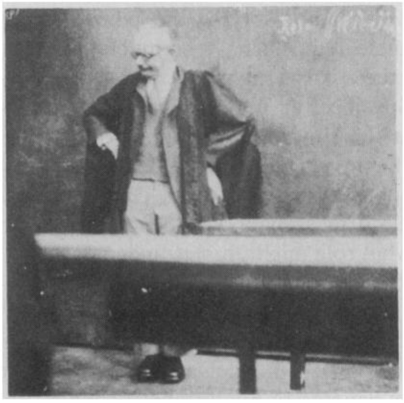
Littlewood Conjecture Resolved

In 1948, British mathematician John E. Littlewood published a surprising conjecture. No matter how clever you are at superimposing sine and cosine waves of different frequencies and amplitudes greater than or equal to 1, he said, you can never get them to completely cancel each other out. In fact, when you add these waves together and integrate, the area they bound approaches infinity as the number of waves being added gets larger and larger.



Ralph Boas, Northwestern University

John E. Littlewood 1938

Littlewood's conjecture has intrigued mathematicians for the past 33 years, in part because it seemed so difficult to verify or disprove and in part because it has applications in harmonic and functional analysis. Progress was made in 1959 by Paul Cohen of Stanford University, in 1979 by John Fournier of the University of British Columbia, and, last year, by S. K. Pichorides, who is visiting at the University of California at Los Angeles. Both Cohen and Pichorides were awarded prizes for their work. But no one was able to show, as Littlewood conjectured, that the integral of the absolute value of the sum of N sine and cosine functions must be at least a constant times the logarithm of N.

Recently, Brent Smith of Illinois State University, Louis Pigno of Kansas State, and O. Carruth McGehee of Louisiana State succeeded in verifying the conjecture. Their paper describing their result has been accepted for publication in the *Annals of Mathematics.* As the three mathematicians are quick to point out, their proof

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is based on Cohen's techniques. But, Pigno explains, they managed to avoid aspects of the problem that had tripped up other investigators. Previously, mathematicians had come across difficult combinatorial arguments when they tried to solve the problem. Smith, Pigno, and McGehee used instead a well-known result from mathematical analysis, the Cauchy-Schwartz inequalities, to solve the problem.

The resolution of the Littlewood conjecture is not, by itself, expected to have a major impact on mathematics. Cohen came so close to resolving the conjecture that most applications followed from his work. "Our paper polishes the thing off and does it with a very simple proof. Its chief value is esthetic," says McGehee. But, says Pigno, "Historically, it's always turned out that new methods have more significance than the original problem. I'm hoping that will happen here."

Russian Proves Van der Warden Conjecture

The Van der Warden conjecture, first published in 1926, sounds seductively simple. "It is so simple to state and to understand. It sounds like it would go in a shot. . . . But it doesn't," says Morris Newman of the University of California at Santa Barbara. Some well-known mathematicians have worked for years on the problem with no success. At least one mathematician at Bell Laboratories was told by her thesis adviser not even to start on the problem because of its difficulty. But a Russian mathematician, G. T. Igorychez of the Kirenski Institute of Physics, Novosibirsk, has finally solved it, using two inequalities proved years ago by another Russian but largely unknown to Western mathematicians. Igorychez's result was published by the Kirenski Institute.

The conjecture concerns the size of the permanent of a matrix, which is the same as a determinant except that all the terms are added together—the signs do not alternate. To form a permanent of an $n \times n$ matrix, mathematicians essentially form all possible products of n matrix entries—one in each row and column. They then add together these $n!$ terms. Permanents of matrices are of major importance in combinatorial analysis, where they tell how many ways one object can be chosen from each of a collection of sets. They also turn up in probability and statistics.

Van der Warden's conjecture involves $n \times n$ matrices, which have the properties that their entries are all nonnegative numbers, the sum of the entries in each column is 1, and the sum of the entries in each row is 1. The conjecture is that the permanent of this sort of matrix is smallest when each entry is $1/n$.

Until Igorychez's result, the best previous result had been obtained in 1961 by Newman and Marvin Marcus of the University of California at Santa Barbara. They showed that for the special case of a symmetrical matrix with nonnegative eigenvalues, the conjecture is correct. After that, says Marcus, "I got tired of the whole thing for a long time. I had spent 3 years of my life on the problem and I figured that was enough." Others continued to work on it, but no real progress was made.

The key to Igorychez's resolution of the conjecture is two inequalities published in 1938 by A. D. Alexandrov in a Russian journal. Marcus says, "The theorem of Alexandrov is very obscure indeed. No one I know has ever heard of it. It was never published in English and the Russian literature of the 1930's is not easy to obtain."

According to Marcus, Igorychez's result is expected to have ramifications in combinatorics. Before the resolution of this conjecture, he says, "many combinatorial problems were up in the air" and others were solved only by ad hoc methods.

Advance in Integer Programming

A Dutch mathematician, Hendric W. Lenstra, Jr., of the University of Amsterdam, claims to have made a major advance in solving integer programming problems—a class of problems that are like linear programming problems except that their solutions must be integers. Lenstra's result, which he described at a meeting in Amsterdam, is being circulated among a few mathematicians and economists, including Herbert Scarf, a mathematical economist at Yale, who says he is sure Lenstra's work checks out. Scarf is especially intrigued with the result because, he says, "Integer programming problems are potentially of great significance in economic theory."

These problems are of central importance to economists looking at production. Current mathematical models of the economy as a whole do not include integer programming problems because they are too difficult to integrate into the models and too difficult to solve. They belong to a class of equivalent problems, including the well-known traveling salesman problem, that seem to have no computationally feasible solutions. But models that do not include integer programming problems must incorporate unrealistic assumptions about production in order to be mathematically manageable—for example, the assumption that large-scale and small-scale production are equally efficient. "Our theories are deficient in recognizing one of the major phenomena of the 20th century," Scarf says.

For the past 20 years, some economists have used integer programming in formulating models of the production side of the economy alone. In these models large-scale production is more efficient than small-scale production. But the models run into trouble because there is no good way to solve the integer programming problems. The difficulty is that as the problems grow bigger, more and more data are required to define them, and the number of computational steps necessary to solve them grows as an exponential function of the amount of data. Although mathematicians and economists have devised algorithms for solving specific integer programming problems, there are, says Scarf, no theorems that would give some insight into the problems.

Lenstra showed that if the number of variables of an integer programming problem is held fixed, the problem can be solved in a number of steps that is only a polynominal function of the amount of data defining it. Although the result does not imply that integer programming problems in general are solvable in this number of steps, it is according to Richard Karp, a mathematician at the University of California at Berkeley, "very surprising. It is quite a step forward."

Gina Bari Kolata