The 1974 Nobel Prize for Physiology or Medicine

The 1974 Nobel Prize for Physiology or Medicine was awarded to Albert Claude, Christian de Duve, and George Palade for their discoveries concerning the structural and functional organization of the cell.

The beginnings of the work for which Albert Claude has been honored are described in papers published by him in the late 1930's. Claude was then an associate of James B. Murphy, whose laboratory at Rockefeller Institute (now Rockefeller University) was engaged in the study of tumor cells and, most especially, cell-free extracts capable of transmitting the tumor from animal to animal. The concentration and purification of the chicken tumor I agent (now Rous sarcoma virus) was at that time the pursuit of several laboratories, and it became Claude's interest to see if he could purify it by differential centrifugation at high speeds. Purify is probably too strong a term; but concentrate it he did, for the final fraction obtained had a tumor-producing activity 50 times greater than the original tissue extract. The fraction had an ultraviolet absorption spectrum with a broad maximum at a wavelength of 2575 Å, and, since the test for pentoses was positive, nucleic acids of the ribose type were thought to be present.

For control purposes Claude decided to compare fractions from chicken tumors with fractions similarly derived from normal chick embryo tissue. In all respects the ultimate fraction from the normal tissues bore a "striking similarity" to the active fraction from chicken tumors except that it failed to produce tumors.

In retrospect this finding appears to have launched Claude into the continuing fractionation of normal tissues and cells of several kinds. The materials that appeared in the fractions were surprisingly similar and had essentially the same physical and chemical characteristics of homologous fractions from chicken tumor I. Cell nuclei, having been removed in the initial brief and low-speed centrifugation, were not a part of the final fractions, and this was confirmed by the absence from them of DNA. Thus, the fractions under study were assumed to include only mitochondria and various other minute components of the cytoplasm. This was in 1939. After 1940, results and observations accumulated with some rapidity and gradually the fraction components were identified with elements in the intact cell.

One can scarcely appreciate the problems that confronted these pioneering attempts at cell fractionation without having been there. There were, for example, no Potter-Elvehjem tissue grinders. Instead the tissue (liver, which had become the material of choice because its cells could be ruptured by relatively mild procedures) was put through an ordinary meat grinder or forced through a sieve. For extracting the tissue brei, a choice of solutions (NaCl, buffer, or simply water) had to be made quite arbitrarily. The centrifuges by today's standards were primitive, somewhat dangerous and limited to a force of about 18,000*g*. The patience of the operator, to say nothing of his determination, was stressed by the inadequacies of the equipment. Fortunately, Claude had these ingredients in his character, and the work went forward.

Separation of Cell Components

From this period there came what is now a fairly standard procedure for the separation of cell components by centrifugation: a short run to remove nuclei and intact cells, and a longer run (1 hour) at higher speeds to separate out the smaller particulates which were then resuspended and washed several times. This fraction, with its phospholipids and nucleoproteins and made up of particles estimated to be 100 to 300 nanometers in size, attracted the greatest attention and was assumed to consist in large part of mitochondria. The supernatants, containing the soluble components and the lighter components of the cytoplasm, were at first not examined with much interest and were sometimes discarded.

Some of the reasoning concerning the identity of the particulates as described now seems confused, but one must remember that there were not in 1940 many consistent observations in the microscopic and submicroscopic components of cells to work from. Studies by Noel on the microscopic anatomy of liver cells, published in 1923, seem to have led Claude into believing that some of the larger particulates from guinea pig liver (0.5 to 3.0 micrometers) were "secretory granules." Actually, liver cells contain no secretory granules in the usual sense, and the larger "secretory" granule fraction was probably rich in lysosomes and peroxisomes or microbodies. The true identity is for present purposes not terribly relevant. What is important is that the methods developed succeeded in isolating them. At this point, Claude extended his methods to a further study of the supernatant, after small-particle removal, and succeeded in obtaining, after several hours of centrifugation, yet another pellet which resembled a "cherry-red" gel; the fraction later turned out to have great significance.

An important digression from the fragmentation-fractionation routine occupied Claude for a while, and this involved him in centrifuging intact tissues and cells. The contents layered out into strata containing glycogen, recognizable mitochondria, "secretory granules," and a layer of amorphous ground substance which was chromophilic. In a report in *Biological Symposia*,* he argues convincingly that the chromophilic substance is the source of his smallest particles and suggests that such particles be called "microsomes." This fraction with its high content of RNA, as it is now known, includes fragments of the endoplasmic reticulum plus attached and unattached ribosomes. In spite of the now-obvious confusion over "secretory granules" and mitochondria in the early attempts at identification there did emerge a clear-cut separation of microsomes from granules of a larger and more discrete nature. Because of the former's content of RNA, Claude argued that they were probably self-duplicating components of the cytoplasm.

It is easy now to recognize that Claude had set the stage technically and conceptually for a whole new area of biological investigation. This splendid piece of pioneering work was not so easy as is the telling of it. He was at first largely alone in the effort and had to face substantial skepticism as to the worthwhileness of studying parts of cells in isolation. It is true also that, as

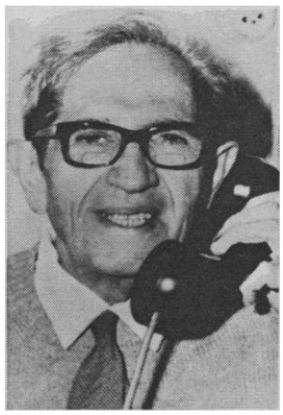
* A. Claude, *Biological Symposia*, (1943), vol. 10.

related here, this subject had its inception with him. That R. R. Bensley, one of the cell biology's most original fathers, had earlier attempted to fractionate the contents of liver cells was apparently not known to Claude until he was well along in the refinement of his procedures. The work published by Bensley and Hoerr in 1934 seems to have been, for them, a one-shot affair.

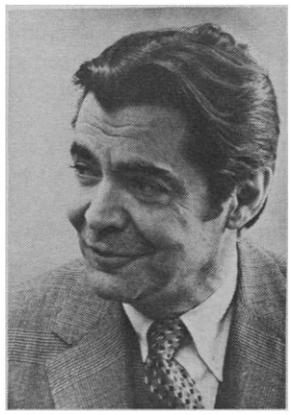
By 1943, Claude was writing about the "Constitution of Protoplasm" with a new sense of authority and certainly from a new point of view. Younger men began to appear in Murphy's laboratory to work with Claude, and one of these, George Hogeboom, with the collaboration of a genuine biochemist, R. D. Hotchkiss, began to take an interest in Claude's fractions. It was not long before the enzyme activities of these fractions were being examined. Cytochrome oxidase and succinoxidase were found predominantly in the large (0.5 to 2.0 micrometer) granule fraction along with less impressive amounts of other enzymes, including catalase and ribonuclease. The smaller particle, microsome fraction appeared to share these enzymes though in far lesser amounts and probably as a contaminant. By this time also, Claude's younger colleagues had convinced him that the large-granule fraction really contained mitochondria, and subsequent publications reported that 70 percent of the cytochrome oxidase and succinoxidase was in the mitochondrial fraction, with lesser amounts in the microsomes and none in the final supernatant.

Claude published in 1946 a summary of his experience in the fractionation of mammalian liver cells, and the study of cell fractions then became the occupation of several biochemists outside the Rockefeller group. This marked the end of Claude's work in this area and Hogeboom, W. C. Schneider, and George Palade picked up where the master had stopped. In 1947, these three introduced the use of gradient sucrose solutions to tissue fractionation, and published conclusive evidence that the large-granule fraction was made up in large part of mitochondria.

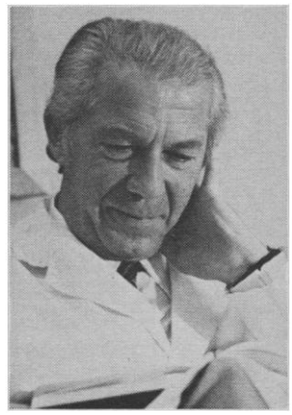
Meanwhile, from 1942 on, Claude had been making short forays into electron microscopy. He received an invitation from the Director of Research, at Interchemical Corporation, to use the only electron microscope then in New York City. Ernest Fullman was there as microscopist and was as valuable to Claude's early successes as the microscope itself. First, the microscope



Albert Claude



George Palade



Christian de Duve

was focused on fractions. Then, with Keith Porter he became interested in looking at cultured cells (which Porter had been trying to grow) because they seemed thin enough for beam penetration. From the images of cultured cells, there came the recognition that the lacework of strands and vesicles (later called the endoplasmic reticulum) in the cytoplasm was the probable source of Claude's microsomes. Finally he made interesting attempts to develop embedding and sectioning technics, and with Joseph Blum designed a microtome which failed in its primary purpose but succeeded in usefully influencing subsequent designs. It must be said with the candor, currently popular, that Claude's work in this area did not hold a candle in its significance to that of his work on centrifugation of cell fractions.

At this point (1949) in his career, Claude took an extended plunge into laboratory administration, which ended for a time his research career. Although he now heads the Jules Bordet Institute in Brussels, Claude has returned to research and is working on the fine structure of various cells and tissues with much of the imagination and enthusiasm that characterized his award-winning studies in cell fractionation.

George Palade would find no offense in being identified as Claude's student. In actual fact, however, his student days, in the strict sense, had ended before he joined the group in James B. Murphy's laboratory at Rockefeller Institute, where he organized and pursued his work on cell fractionation and electron microscopy.

Palade received his training in classical histology and histophysiology in Romania and, in terms of actual experience, was well prepared to make full use of the combined procedures of fractionation and electron microscopy. This was evident in the first work with George Hogeboom and W. C. Schneider on the identification of large granules with mitochondria and became increasingly evident as he began his collaboration with Philip Siekevitz. Palade's career at Rockefeller Institute and University where he worked for 28 years was a continuous series of firsts which have survived and are likely to survive forever. These discoveries and observations have had an enormous impact on cell biology in the exciting period of its development since World War II. Palade has been able as few others have been to assign functional significance to structural information superbly recorded.

Fixation of cells for microscopy was for him an obvious and essential place to begin. The faithful preservation of cell form by vapors of osmium tetroxide applied to cells in vitro had been known for several decades and was reestablished by electron microscopy of cultured cells then being done in Murphy's laboratory. However, this quality of fixation was not achieved when osmium tetroxide was used on cells in blocks of tissues. The reason for the difference was not apparent, but Palade suspected that the buffer contained in the balanced salt solutions used on the cells during exposure to osmium tetroxide might be significant. Out of this reasoning and some related experiments there grew the introduction of buffered osmium tetroxide as a fixative, and from its use came a wealth of the early microscopy of thin sections. It was the recipe of choice for 10 years until replaced by glutaraldehyde as a fixative, also buffered.

With this and the techniques for em-

bedding in methacrylate and sectioning with glass knives on improved microtomes the doors to cell and tissue fine structure were opened wide. Palade was one of the first to enter and for a time it was a race with Fritiof Sjöstrand, among others, to see who could discover the most. It was in this period around 1951–1952, that Palade made his definitive study on the fine structure of mitochondria. Here for the first time one could really see these organelles and, moreover, observe their internal structure. In this pursuit he investigated beyond the liver and kidney and was thus able to show that mitochondria in all cells are limited by two membranes and that the inner of the two membranes projects as folds or shelves into the intramitochondrial matrix. To this kind of shelf he applied the name crista.

These discoveries seemed to stimulate more microscopy, and before long other components of the cytoplasm began to be understandable. With Keith Porter he began a series of studies on the cytoplasmic membrane systems out of which there came the recognition that the endoplasmic reticulum, as it was called, is present in all eukaryotic cells, although in greatly varying organizations. In muscle its precise distribution relative to the myofibrils and sarcomeres suggested a participation in the phenomena of contraction.

Within a couple of years of these preliminary adventures in electron microscopy, Palade had made one of his most important observations. This was that "a granular component of small size and relatively high electron density appears regularly in the cytoplasm of various cell types." In some cells, particularly those involved in the synthesis of protein for secretion, they were found attached to the outer surfaces of the membranes limiting the endoplasmic reticulum. In others, such as the rapidly growing cells of embryos where the synthesized protein is retained, the granules or particles were observed to be free in the cytoplasm. There, association with the property of basophilia (affinity for basic dyes) shown by the cytoplasms of various cell types was quickly recognized. It was also evident that they might be rich in RNA and have something to do with protein synthesis.

These discoveries and speculations, on what were later called ribosomes, marked the beginning of Palade's studies on protein synthesis, studies that turned out to be the major interest of his scientific career. At this point, Palade recruited Philip Siekevitz, a biochemist, and together they began a series of studies on liver and pancreatic microsomes and on protein synthesis in the pancreatic cell, studies which will remain important for all time.

In each instance the experiments achieved an integration of morphological and biochemical information. Inevitably, the studies focused on the ribosome, its structure, and its relation to the synthesis of proteins.

By 1960, the story was quite clear: the digestive enzymes of the pancreas are synthesized in or on the ribonucleoprotein particles (ribosomes) and then sequestered in the cisternae (internal spaces) of the endoplasmic reticulum for transport to storage sites preparatory to secretion. This sequence of intracellular events was substantiated shortly thereafter in autoradiographic studies with Lucien Caro. Tritiated leucine injected into guinea pigs was incorporated within a few minutes into proteins in that part of the cell occupied by ribosome-rich forms of the endoplasmic reticulum (ER). From there, the labeled protein was followed through the channels of the ER and eventually into the secretory granules in the apical poles of the exocrine cells. The study was one of the most impressive of its kind up to that time and left no doubt as to the site of synthesis and subsequent movement of pancreatic enzymes.

The Ribosome and Protein Synthesis

The ribosome then became reasonably an object of great fascination, with more detailed questions as to its structure and the nature of its involvement in protein synthesis. New collaborators recruited for these investigations included David Sabatini, C. Redman, and Y. Tashiro; through their association with Palade, it became known that the larger of the two ribosomal subunits is attached to the membrane and is the site of amino acid assembly into polypeptides. Simultaneously, J. D. Jamieson and Palade were exploring the intracellular transport of pancreatic enzymes from synthesis to storage. This work established the involvement of vesicles from the Golgi complex, especially in the final stages of storage.

To recount all of George Palade's observations on cells and their functions would require a great deal of space. His skill and his enthusiasm for unraveling the intricacies of the fine structure of cells attracted many students and research associates to his laboratory. The research reports of these associations appeared parallel to those from the mainstream of protein synthesis and covered a wide range of important topics.

There is seemingly no letup in the pace at which new and important observations emerge from the Palade laboratory (now at Yale University), and it is unlikely that this latest recognition of his achievements will affect this productivity. Obviously, original discovery is the native bent of some people, and the compulsion to go on and on seems not to diminish with age.

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During the years 1939 to 1961 Keith R. Porter collaborated with Albert Claude and George Palade at Rockefeller University on much of the work described above.

"The lysosome," de Duve wrote in 1969, "introduced itself to us on December 16, 1949." He continued, "The introduction was far from explicit, taking in fact the suitably cryptic form of latent acid phosphatase. It was also importunate, since it held not the slightest relationship to the final goal of our research, which happened to be the demonstration of an effect of insulin on isolated liver tissue." Acid phosphatase activity in a mitochondrial fraction isolated on that day was strikingly less than when the fraction was tested again 5 days later. What might readily have been disregarded as a disturbing or meaningless result led de Duve to search for its deeper significance. He deduced that most of the acid phosphatase activity was in "latent" form in well-prepared fresh fractions but expressed itself when the fractions aged. He and his collaborators at l'Université Catholique de Louvain (including among others Jacques Berthet and Robert Wattiaux) assayed a variety of enzyme activities in the heavy mitochondrial (M), light mitochondrial (L), and microsomal (P) fractions isolated from rat liver homogenates by differential centrifugation. Five acid hydrolases (and urate oxidase, to which I will return later) were found in highest concentration in the L fraction. Since these activities were not consistent with those of mitochondria or microsomes, it was proposed that the hydrolases were bound in a postulated cytoplasmic organelle, the "lysosome."

On the basis of sedimentation behavior, the Louvain investigators calculated that the diameter of hepatic lyso-

somes "must range mostly between 0.25 and 0.8 μ if their density is low (1.10) or between 0.13 and 0.4 μ if their density is high (1.30)." They soon concluded that their density was high. From the latency of all five hydrolases they reasoned that the organelles were "surrounded by a semipermeable membrane." From measurement of the nitrogen content of the L fraction, they inferred that the lysosomes "must be very few" in number, accounting for "4 percent or less of the cells' nitrogen." Subsequently, in a collaborative effort with de Duve and Henri Beaufay in Louvain, Albert Claude in Brussels, and Wilhelm Bernhard in Villejuif, outside Paris, I did indeed find by electron microscopic examination of the L fraction an organelle about 0.4 micrometer in diameter and surrounded by a tripartite membrane. The organelle resembled the "pericanalicular dense bodies" described in rat hepatocytes by Charles Rouiller in 1954. Acid phosphatase cytochemical studies by Stanley Holt and Marian Hicks in London, and by others, soon confirmed our tentative identification of the dense bodies as the hepatocyte lysosomes. Sagacious deduction from biochemical data by de Duve was thus confirmed by morphologic findings—a startling reversal of the usual course of events.

A flood of publications followed, including studies with electron microscope cytochemistry. Lysosomes were found to be ubiquitous in animal cells. They were shown to exist in several different cytologic forms. In symposiums held in 1959 at the Marine Biological Laboratory, Woods Hole, and in 1963 at the Ciba Foundation, London, de Duve discussed a wide variety of possible functional roles for lysosomes. The two-volume work, *Lysosomes in Biology and Pathology*,* edited by John T. Dingle and Dame Honor B. Fell, summarized the status of the field in 1969.

De Duve's remarkable mind is reflected in his hesitation to assign urate oxidase to the same cytoplasmic particle that houses the acid hydrolases. In the initial experiments this oxidative enzyme activity sedimented with those of the hydrolases, but some minor differences in its behavior made de Duve consider that this nonhydrolase might be localized in yet another cytoplasmic organelle. Urate oxidase (and two other enzymes related to the production and breakdown of hydrogen peroxide) were later shown by de Duve, Pierre Baudhuin, and others in the Louvain group to be localized in a different organelle, the "peroxisome." The preparation of

* North-Holland, Amsterdam and London.

Laser Fusion Secrecy Lifted: Microballoons Are the Trick

For the first time, at a conference in Albuquerque, New Mexico, last week, scientists without security clearances were able to learn most of the intimate details about the government's $66 million research program aimed at producing power by laser fusion.

The laser fusion program was almost totally classified in the early stages, apparently because of its potential for development of nuclear weapons and for simulation of weapons effects, cited in official Atomic Energy Commission (AEC) statements. Other scientists have hinted that laser fusion was classified not so much for its military usefulness as for the similarity of certain laser fusion calculations to the design studies for an H-bomb. Several well-known physicists, including Edward Teller, at the Lawrence Livermore Laboratories of the AEC, and George Trigg, editor of the *Physical Review Letters*, have argued that classification of laser fusion was unnecessary and detrimental to efficient research on the subject.

Guidelines for public information were relaxed slightly in 1971. But most of the research, particularly the details of the fuel pellet, remained secret. The big change occurred on 28 August after a thorough review of the classification guidelines during the past summer.

Laser fusion is based on the idea that a very high powered laser focused on a very small spot could heat a pellet of fuel above the 10^7 degree minimum temperature needed for fusion to occur. Before the disclosure of the implosion concept in 1971, no way was known to achieve the required conditions without an impossibly large laser. Public reports and conversations with scientists in private suggested that the design of the fuel pellet was crucial to the success of the implosion scheme. It was hinted that the laser target was perhaps a liquid droplet, a solid frozen pellet, or a hollow sphere. The new information shows that all suppositions were wrong.

Laser fusion researchers in the government and in private industry have been firing their lasers, or planning to fire them, at tiny hollow glass spheres called microballoons which enclose the fuel. Produced by commercial glass manufacturers in lots of at least 2 million to the kilogram, these small spherules provide a casing that keeps the fuel from leaking out as the whole assembly undergoes compression. The actual fuel, which is a mixture of equal parts of deuterium and tritium, is introduced into the microballoons as a gas in sufficient quantities to reach a pressure of 50 to 100 atmospheres.

In order to introduce the gaseous fuel into the glass balloons, which are only 50 micrometers in diameter, the glass spherules are placed in an oven and heated to 500°C. At that temperature gas diffuses easily through glass, and so the isotopes of hydrogen that make up fusion fuel rapidly migrate inside and are trapped there when the microballoons are quickly cooled. Millions of glass balls are tested and sorted in order to find those without imperfections, and even so the shelf life of microballoon targets is limited because the gas fuel tends to diffuse out.

Different variations on the microballoon targets are undoubtedly used at different laboratories, but generally some sort of outer layer is added. Some material is needed around the microballoon to absorb the energy of the laser pulse and ablate, driving the glass sphere and its trapped fuel inward as the ablating material expands outward. The microballoon must have a fairly high atomic number, relative to hydrogen, to trap the gaseous fuel, but the outer material must have a low atomic number to be a good thermal conduction medium. Microballoons may be coated with plastic, which has a satisfactorily low atomic number, or they may be mounted on a backing of some other low-Z material.

—WILLIAM D. METZ

lysosomes and peroxisomes, each in highly purified fractions, required the more refined means of centrifugation which resulted from theoretical considerations and technical advances by de Duve and his colleagues, mainly Berthet and Beaufay. In 1969—by which time de Duve had established a flourishing Department of Biochemical Cytology at the Rockefeller University while continuing to lead his Department in Louvain as well—he organized a meeting which was sponsored by the New York Academy of Sciences on the various roles of peroxisomes in animal and plant cells.

Early in its work the Louvain group undertook the study of "storage diseases" of man; this study was under the leadership of Géry Hers, who had collaborated with de Duve since the earlier studies on insulin and glucagon. *Lysosomes and Storage Diseases*,† edited by Hers and François van Hoof and published in 1973, describes some 30 diseases, characterized by deficiencies of single lysosomal enzymes.

In recent years Christian de Duve turned his attention increasingly to lysosomes in cell pathology and disease and to lysosomes as targets for drugs. He refers to drugs acting via their effects upon lysosomes as "lysosomotropic." One of his groups in Louvain, led by André Trouet, has already obtained encouraging results in cancer chemotherapy. This group complexed the antibiotic, Daunomycin, with DNA and thus reduced its toxicity. Pinocytosis brought the complex into the lysosomes of the cancer cells, and the hydrolases removed the DNA and released the active antibiotic. In de Duve's laboratory at Rockefeller University interesting findings have been made on atherosclerosis. These suggest that abnormal lipid accumulations in aortic smooth muscle cells result from a relative deficiency in acid lipases that hydrolyze esters with long-chain fatty acids.

Rarely has a domain of cell biology or cell pathology been influenced so profoundly by a single intellect as has the lysosome-peroxisome field.

Last year an attractive book appeared which described the new International Institute of Cellular and Molecular Pathology organized by de Duve and his Louvain colleagues and just constructed in the outskirts of Brussels. On its first page is reproduced the title page of the great 1862 classic by Rudolf Virchow, "Die CELLULARPATHOLOGIE in ihrer Begründung auf physiologische und pathologische Gewebelehre." De Duve concludes the introduction in these words: "No longer held back by the impassible boundaries of the cellular world, medical research can now gain full entrance to the cell, if it allows itself to be guided by modern cellular and molecular biology. The latter disciplines, in turn, have the duty of providing medicine with the means of accomplishing this objective."

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† Academic Press, New York, 1973.

Analysis of Algorithms: Coping with Hard Problems

Although today's computers can perform as many as 1 million operations per second, there are many problems that are still too large to be solved in a straightforward manner. Even with improved solution methods, or algorithms, exact solutions to a wide range of practical problems, from routing of phone calls to scheduling of airplanes, require weeks or months of computer time and are, in effect, not feasible to obtain. Hence the investigation of still more efficient algorithms is of interest to large companies as well as to computer scientists.

The task of finding good ways to solve a large group of important problems has recently, in theory, been simplified. It was shown that many such problems are computationally equivalent, so that a solution for one of them can be used to solve the rest. For example, the problem of determining the best way to schedule events can be converted into the problem of finding the best way to store objects in the minimum amount of space. However, these equivalent problems have so far defied all attempts to solve them without using inordinate amounts of computer time. Since these problems are of great practical importance, many investigators are now devising ways to approximate their solutions and, in some cases, are showing how close certain approximations come to optimum solutions to a problem.

In their search for a good algorithm, computer scientists try to avoid those algorithms in which the number of computational steps (or the amount of computer time) is an exponential function of the size of the problem. (The size of a problem is essentially the number of bits of information required as input for the problem.) Since exponential functions increase very quickly as the size of the problem grows, such algorithms are said to be "inefficient."

The ideal algorithm is one in which the number of computational steps increases only as a polynomial function of the size of the problem. Such algorithms are said to be "efficient." The difference between an efficient and an inefficient algorithm can be dramatic. For example, one algorithm for a problem of size n might require n^2 steps (a polynomial function) while another might require 2^n steps (an exponential function. When n is increased from 10 to 20, the number of steps of an algorithm that requires n^2 steps will quadruple, whereas the number of steps of an algorithm that requires 2^n steps will increase more than 1000-fold.

A few years ago, Stephen Cook of the University of Toronto analyzed several difficult problems for which no efficient algorithms are known. He showed that all these problems are computationally equivalent in that an efficient algorithm for one of them, if it exists, could be used to solve them all. Richard Karp of the University of California at Berkeley then extended the list of equivalent problems to include many examples in such fields as network optimization, graph theory, and scheduling. Computer scientists decided to call these problems NP-complete. (The symbol NP stands for nondeterministic polynomial time. Complete indicates that a solution to one problem could be applied to all others in the set.)

No one has yet proved that efficient algorithms exist for the NP-complete problems. Many computer scientists