*Massachusetts Institute of Technology has birthed more companies than any other university. Now it is finally starting to collect some of the payoff.*

# Patent profit

**By Laura Jereski**

LAST YEAR John Preston filed at least 100 different patent applications. This year he expects to file 150 more. Restless genius? Not quite. Preston, 38, heads the technology licensing office at Massachusetts Institute of Technology. His mission: to find commercial outlets for the inventions and innovations born in MIT's labs—and to make a little money for the university, besides.

Just keeping up with MIT's output is no small task. At $300 million for fiscal 1988, the celebrated Cambridge, Mass. school's on-campus research budget is 50% more than neighbor Harvard's. Add the $400 million or so at Lincoln Laboratories, the electronics center MIT runs for the U.S. government, and the fuel research at the nearby Whitehead Institute, a biomedical research affiliate, and MIT's research budget outstrips that of any other American university.

No wonder so many companies have been founded by alumni or professors, many based on technology discovered in the school's labs: at last count, more than 400 firms in Massachusetts alone, with revenues last year of $27 billion. These include not only such giants as Digital Equipment Corp. and Raytheon, but also some relative newcomers like Lotus Development Corp., Prime Computer and Symbolics, the artificial intelligence company.

And where was MIT? Standing idly by, neither helping the ventures get started nor getting much benefit from their success. Now John Preston, himself a cofounder of a software company, is changing that. Through his technology licensing office, MIT is beginning to work more closely with companies that will use its lab-bred innovations. And he wants the school to help set up companies based on new technologies.

One of the first things to be done was to get rid of two of the three lawyers running the licensing office set up in 1932 to file and manage MIT's patents. Says Preston, "They were great at protecting the scientists and lousy at marketing their inventions." No kidding. When he took over in mid-1986, royalty income had stagnated at some $2 million annually. For a good part of the past 20 years, most of this income had derived from two discoveries—synthetic penicillin and magnetic core memory for computers. Licensing had virtually ground to a halt.

Seth Resnick/Picture Group

*MIT's John Preston*
***"We've changed the professors' mentality."***

By the end of 1987, Preston's first full year, licensing revenues hit $3.1 million from about 100 inventions, both new (high-temperature superconductors) and old (LISP, the software of choice for so-called artificial intelligence computers). With license fees ranging from 2% to 6% of net revenues, depending on the product, some $150 million of products manufactured last year—including expert software and new drug delivery systems to treat brain tumors—depended on processes developed at MIT. Only Stanford (with license revenues of $6.1 million), the University of California ($5.4 million) and apparently the University of Wisconsin (about $5 million) do better.

Preston is predicting royalty revenues of perhaps as much as $50 million in another five years. How? "We've changed the professors' mentality," says Preston proudly. "They've started thinking, 'If I can show commercial results, I'll have a better shot at raising my research funds.' They've changed away from pure scientific research."

Indeed, the school itself has changed. Now, when a really good technology comes along, Preston helps the inventor set up a new company—and often takes a small chunk of equity as part of the licensing fee.

Each invention is screened by a committee of six, which includes three engineers and three scientists. When this group is unsure, they turn to medium-size high-tech companies to see what they think.

Last year Preston's technology office acted as marriage broker between venture capitalists and the largest new startups in Boston: American Superconductor (initial capital, $4.5 million) and Immulogic Pharmaceutical ($3.25 million). The technology office owns roughly 10% of each company.

Underlying such opportunities is a change in federal law in 1980 that gave universities ownership of federally funded intellectual property. (Such property had belonged to the government.) Since then, industry contributions to universities have taken off. Between 1980, before the law changed, and 1986, research funds from companies nearly tripled, to $667 million. And MIT, of course, gets far more every year than any other school: $37 million in 1987 alone. Will MIT begin to fund its spinoffs directly or perhaps set up incubator parks to coddle them? Not likely, says Preston. "You have to let the free market decide which are the better ideas," he says.

But at least you ought to get a piece of the action. ■

*Continuation of Senate Proceedings of November 21, 1985, Issue No. 161; and Proceedings of November 22, 1985, Issue No. 162.*

United States of America

# Congressional Record

PROCEEDINGS AND DEBATES OF THE 99th CONGRESS, FIRST SESSION

*Vol. 131* WASHINGTON, THURSDAY, NOVEMBER 21, 1985 S 16229

# *Senate*

*(Legislative day of Monday, November 18, 1985)*

## MEETING INTERNATIONAL COMPETITON WILL TAKE MORE HELP FROM SMALL BUSINESS

● Mr. KERRY. Mr. President, as a member of the Senate Small Business Committee, and its Subcommittee on Innovation and Technology, I would like to call attention to some of our accomplishments, and as some of the goals that remain unmet.

I believe that we can take pride in the fact that the committee was the first to advocate a government-wide small business innovation research program, and that the Senate took the initiative in the enactment of the Small Business Innovation Development Act in 1982 (Public Law 97-219).

We can also derive satisfaction that the 11 Federal departments and agencies participating in the program, and the community of small techology based companies in this country have made this program a ringing success. That is the good news.

The bad news is that in 1977, before the SBIR program was extended to all Federal agencies, a Presidential study found that the small business share of Federal research and development funds was approximately 3½ percent. For fiscal 1984 the small business share of those funds was 2.91 percent, according to a recent SBA [Small Business Adminstration] report (See "Second Year Result Under the Small Business Innovation Development Act of 1982" Report No. 453, March 15, 1985, exhibit 3-6, page 26).

I believe this decline is unfortunate in view of the conclusions of the 1977 study that: First, small business had consistently accounted for half of all industrial innovation, second, this constituted "a striking record of innovation"; and third, that small technology-based enterprise deserved greater Federal research and development support as a way to strengthen the innovation process in this country.

### LEGISLATIVE HISTORY

In 1978, the Senate and House Small Business Committees held joint hearings on the utilization of small business enterprise in solving the nation's technology problems. The evidence was that executive departments and agencies, such as the National Science Foundation, NASA [the National Aeronautics and Space Administration] and the Defense Department, which has increased small business R&D funding, were better able to fulfill their mission responsibilities. (See 29th Annual Report of the Senate Small Business Committee, Senate Report 96-31, page 144.) These hearings and the consequent joint report of the two committees (Senate Report 1413, December 28, 1978) became the foundation for the enactment, in 1982, of the Government-wide SBIR program under the leadership of the Senator from New Hampshire [Mr. RUDMAN], and the Senator from Connecticut [Mr. WEICKER].

### SUCCESS OF THE PROGRAM

The SBIC legislation provides that each Federal department or agency with extramural research budgets exceeding $100 million should participate in this program, and 11 departments and agents doing so. In response to their solicitations, they have, over the past 3 years, received approximately 25,000 SBIR research proposals aimed at solving technical problems which they need to surmount to better perform their assigned missions.

In fiscal year 1983, the agencies solicited proposals on 618 topics and made 686 awards. In 1984 the number of topics had grown to 1,650 and the agencies had made 999 phase I awards (up to $50,000 to illustrate the technical feasibility of the innovation) and 338 phase II awards (up to $500,000 to bring the project to a proto-type or pre-production stage). These figures are derived from testimony by Richard Shane, Assistant Administrator of the Small Business Administration, in hearings before the Subcommittee on General Oversight, House Committee on Small Business November 6, 1985, conducted by Representative MAVROULES.

### MASSACHUSETTS RANKS SECOND IN THE NATION

I am proud to say Massachusetts is the second ranking State in the number of awardees. For the first 2 years of the program, that is fiscal year 1983 and fiscal year 1984, California had received 416 awards for a total dollar amount of $36.4 million, while Massachusetts had won 337 awards for a total amount of $30 million. The quality of awards originating in Massachusetts is indicated by the high proportion of proposals from the Bay State that are successful under the program. The so-called "Route 128" technology based firms are thus making signal contributions to our national research and development and I salute our Massachusetts entrepreneurs for their efforts.

Interest in the program on the part of small technology-based firms remains high. I understand that the interagency SBIR orientation conference scheduled for November 25 and 26, 1985 at the Marriott Copley Place in Boston has attracted over 800 attendees. These conferences are obviously filling a need. I congratulate the National Science Foundation, the Energy Department and other Federal departments and agencies for organizing these events, and wish the Boston conference well.

Thus, in my opinion, the SBIR program is proving to be good for the country and good for the State of Massachusetts.

A notable aspect of the program is its marriage of public and private sector judgment. When firms submit their applications for phase II awards, the determining factor is the applicant's ability to obtain a private venture capital commitment. What this means is that if the innovation meets its specifications, the private money will be invested to produce the innovation for the commercial marketplace.

Another aspect is that SBIR does not cost the taxpayer any additional money. It sets aside a percentage—up to 1.25 percent in the final year—of whatever the agency budget happens to be for this SBIR type of competitive procurement. About 1 out of 12 proposals wins a phase I contract or grant. I believe these features make a lot of sense and we should commend the designers of this program as well as those in the Congress who recognized the merit of this system and guided the program to enactment.

SBIR ALLOWS VERY SMALL FIRMS TO COMPETE

Among the consequences of SBIR is to keep alive the spirit of Yankee ingenuity, and to open the doors of massive Government agencies to the very small firm which may have an idea that can revolutionize an industry. For example, of the companies funded by one prominent Government agency, 48 percent were less than 5 years old and 44 percent had fewer than 10 employees (Business Week, October 22, 1984, page 146.) Such small firms do not have the teams of engineers, administrators and lawyers to deal with book-sized bidding instructions from Federal agencies or to put together lengthy contract proposals. Under the SBIR program, all phase I proposals are limited to 25 pages. It is encouraging to note the report from the same article that Federal agencies, after initial fears that they would have to deal with hundreds of small inexperienced bidders, now say that they are getting "two worthwhile proposals for each one they can fund." SBIR funds help the firms to grow into better competitors.

VALUE OF SBIR TO LARGE CORPORATIONS AND UNIVERSITIES

The program has proven good for large businesses. One study indicates that more than 40 percent of the SBIR winners expect to develop one or more of its innovations in some sort of licensing arrangement, or joint venture with a larger firm. (Venture Magazine, November 1985, page 148.)

The program has also been good for universities. Business Week also reported that a significant proportion of the proposals funded are "university-coupled," that is using university professors as consultants or subcontractors for research or facilities. In some agencies, the share is well above 50 percent.

Business Week also reported the universities, which initially opposed the SBIR program as competition for Federal research money, will now admit that the program "is working well." Since the Federal research budget for the current fiscal year is approximately $53 billion, and the amount allocated to SBIR is approximately $200 million, the SBIR share of total Federal research dollars amounts to less than one-half of 1 percent. That is not much competition, especially in an era of rapidly rising research budgets. Yet, despite the miniscule participation of small high-tech firms in federally funded R&D, small business innovations have played a critical role in the American economy.

THE NEED FOR BETTER INDUSTRIAL COMPETITION AGAINST IMPORTS

Our adverse trade balance is sending us messages that the United States is now in a global market, and we are losing out in international competition in many areas.

This is not the fault of our efforts in pure scientific research in this country. The efforts of U.S. universities and nonprofit organizations have, in fact, been the envy of the world. Our researchers have won part or all of 87 Nobel Prizes in physics, chemistry and medicine while the Japanese researchers have won only 4 such prizes. The state of our pure research is excellent, and we should continue to support and expand it.

However, what is not so good is the state of our applied research. What we need to improve as a nation is translating the results of our magnificant pure research into commercial products that can be sold in the marketplace, both here at home and in world export markets.

The innovation process, by large and small companies, is the bridge over which these research results travel to enter the market place. Small business accounts for half of the traffic. Examples of small business innovations include the xerox process, the instant camera, the helicopter, the catalytic cracking process for oil refining, hand-held calculators, mini-computers, and hundreds of others.

Our need for more commercial innovation is demonstrated by the trade balance of the United States over the past decade. For the 5 years from 1976 to 1980, the international balance of payments on goods and services, which includes all investment transactions, services, travel and transportation receipts—but not pensions and other transfer payments—amounted to a net surplus of $2.6 billion. For the years 1981 through the first half of 1985, the U.S. goods and services balance was a net deficit of $164.4 billion. High technology products have been an incresing proportion of U.S. exports.

The influx of foreign goods into the United States is beating the socks off of traditional mainstay American manufacturing industries such as steel, automobiles, TV, shoes and textiles. For example, in the past month General Electric Co. has closed its last television manufacturing facility in this country.

I believe that our inability to compete with imports in many of our traditional industries has become a crisis for the U.S. economy. If we hope to turn that balance of payments around, we need more innovation from large and small business. Experience such as the SBIR program indicates that increased support for small business will help us meet the international challenge by bringing more innovation into production sooner.

THE NEED FOR MORE JOBS IN THIS COUNTRY

Another consequence of the adverse balance of payments is that the United States is loosing jobs.

Although the number of jobs in our economy set records in 1984 and 1985, job creation did not keep pace with our needs. Unemployment still came to 8¼ million in 1984 and "part-time employment for economic reasons" added another 5½ million, a total of more than 12 percent of our labor force which is not fully utilized. (Economic Indicators, Joint Economic Committee, October, 1985, page 11.) Further, a thoughtful report entitled "The Future of Work" has predicted that "4 to 6 million jobless workers may become part of a permanent labor surplus * * *." if action is not taken to attack the Nation's unemployment problems. (A report by the AFL-CIO Committee on the Evolution of Work, August 1983). I am concerned over the present unemployment situation and the potential of even greater problems in the future.

THE VITAL ROLE OF SMALL BUSINESS

However, some of the best news in the job market in recent years has come from small business. In 1981 and 1982, small independent firms created 2,650,000 new jobs, while the rest of the economy was loosing 1,664,000 jobs. The overwhelming proportion of those jobs were generated by small, independent private enterprise businesses with less than 100 employees. These are not only high-tech firms, but medium-tech, low-tech and no-tech firms as well. But, of course, the firms that are developing new innovations and products and new industries have the greatest history of and potential for job creation.

TEAMWORK CAN HELP ACHIEVE THESE GOALS

My point is that we need teamwork and balance among all elements of American society—large businesses, small businesses, universities, nonprofit organizations and a knowledgeable government. There is a place for all. Especially in light of the experience in my own State of Massachusetts, and the national and international evidence, I am convinced that programs such as SBIR, which permits the small business community to attain a higher degree of Federal research support, help the country quicken the innovation process. In turn, this can help our national competitiveness and job creation in the years ahead.●

NEXT

# Chance and drug discovery

Further tales of the exploits of the Prince of Serendip.

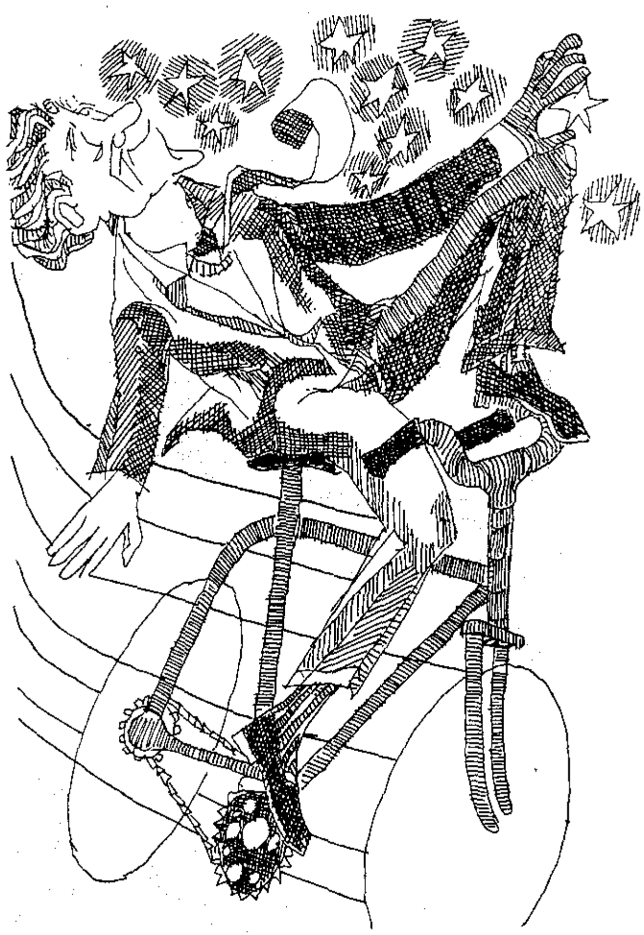
**Patrick J. Hannan**
**Rustum Roy**
**John F. Christman**

In our last CHEMTECH article (*1*), we showed how creative researchers transformed lucky accidents into modern materials. Now let's see how medicine and the pharmaceutical industry benefited from serendipitous discoveries.

Most of us have been told how Pasteur picked apart by hand his *d*- and *l*-tartaric acid crystals, which fortuitously had been prepared under conditions that did not give the *meso* form. Unlike some lesser students, he didn't discard his crystals, even though they didn't conform to those described in his book.

Most of us have also read how Alexander Fleming's chance discovery of penicillin lay dormant until Howard Florey by chance rediscovered it. But there's more to the penicillin story (*2*).

Penicillin was so scarce in 1940 that it was often extracted from the urine of a treated patient and used again. A fortuitous circumstance brought the team of Florey and Norman Heatley from Britain to the Peoria, Ill., lab of the U.S. Department of Agriculture. Florey's fermentation process yielded only a 0.0001% return, and his initial thought was simply to scale up that procedure. But the head of the Peoria lab argued that all efforts should be directed to improve the yield. The fortuitous accident of time and place was that the Peoria laboratory had been looking for industrial uses for surplus cereal crops. A major problem was disposing of the viscous corn-steep extract that was a byproduct of soaking corn in a sulfite solution. Every conceivable use for this liquor was being sought, and that's why some of it was added to the penicillin cultures, resulting in a surprising doubling of the yield. Even more surprising was the fact that a mold on a cantaloupe bought at a local market gave a better penicillin yield than any strain found anywhere else. Other elements were involved in the optimization of the yield, but the choice of Peoria as the site for the work was the serendipitous event of prime importance.



Ronald Rossman (*3*) tells the following three stories:

- The use of iodine in the treatment of Graves' disease was discovered when Trousseau absent-mindedly prescribed tincture of iodine for a patient with a rapid heartbeat resulting from the disease; the iodine worked, but Trousseau had meant to prescribe the tincture of digitalis.
- The effectiveness of phototherapy in treating lupus, a skin disease, was discovered accidentally by a Berlin watchmaker, whose symptoms of lupus were cured after using high-powered lenses near a window.
- "Pap" smears used in the early detection of cervical cancer originated from George Papanicolaou's study of the cellular content of vaginal smears as a function of the reproductive cycle. He discovered many cancerous cells during his investigations and concluded that the procedure could form the basis for an early warning signal for cancer.

An understanding of which hemisphere of the brain controls consciousness resulted from a chance observation by Leo Serafetinides (4) as he studied epileptic patients. He examined epileptic patients using the intracarotid sodium amytal test for the cerebral dominance for speech. In this test, one injects sodium into one carotid artery at a time and then observes the effects on speech and on motor and sensory functions. Serafetinides became gradually impressed by the fact that, in addition to these functions, consciousness was also affected. Sodium amytal produces a coma. It was assumed at the time that the duration of the coma depended on the patient. Serafetinides noticed that when the sodium amytal was injected into the dominant hemisphere for the function of speech, the coma persisted longer than when it was administered to the other hemisphere. This has since led to a theory of cerebral dominance for consciousness paralleling that of speech.

LSD was discovered by Albert Hoffman (5) when he accidentally ingested some of the compound and, after noticing that he was not feeling well, bicycled home with some difficulty. Upon returning to the laboratory the next day, he systematically tasted every compound with which he had had contact until he was certain which one was responsible for the effect.

Disodium chromoglycate is effective in the treatment of asthma (6), a condition in which airways of the lung (bronchi) are narrowed; this narrowing can be due to mucus, swelling of the lining of the airways, spasm of the muscle in the walls of the airways, or a combination of these factors. A small team of researchers at the Benger Laboratories in Cheshire, England, was searching for a novel bronchodilator drug and, for a starter, was interested in khellin, a naturally occurring compound that dilates blood vessels. Khellin is a smooth muscle relaxant but has unpleasant gastrointestinal side effects. In the early 1950s the Benger team demonstrated that synthetic derivatives of khellin protected guinea pigs from the effects of bronchoconstrictor substances such as histamine and acetylcholine. At about this time, Roger Altounyan, physician and a chronic allergic asthmatic, joined the team and was curious to know whether the test results found with guinea pigs could be reproduced in man, namely, himself. In his own words: "I could see nothing in common between guinea pigs and man except that neither species wagged a tail." He ultimately found that one of the khellin derivatives exerted a protective effect against bronchial allergen challenge without showing a relaxant effect on smooth muscles or having antihistamine properties. What's more, the compound was ineffective in the guinea pig tests.

The research paid off because one man wanted to know whether a guinea pig was more reliable than he as a test organism. A quote from Altounyan: "Beware of the expert; by the time he is generally referred to as such, in my experience, he should usually be referred to in the past tense."

An insight into the mechanism of Parkinson's disease resulted from the sloppy laboratory practices of a man synthesizing heroin-like drugs in northern California. As told by Roger Lewin (7), a 42-year-old drug addict was admitted to Santa Clara Valley Medical Center in San Jose with symptoms of Parkinson's disease, but neurologists Philip Ballard and William Langston hesitated to make that diagnosis because Parkinson patients were generally older than this man. A week later, the man's sister was also admitted with similar symptoms. Fortunately, Ballard was invited to a party at a friend's home in Santa Cruz where he met and talked with a neurologist from nearby Watsonville who had a young patient who had suddenly become rigid and immobile. Like the San Jose patients, he was a drug user and had recently obtained synthetic heroin. The doctors decided to quickly publicize the dangers of the new drug and sent samples to several forensic laboratories. A toxicologist named Halle Weingarten recalled having read an article in a little-known journal about a 23-year-old graduate student who had developed a Parkinson-like condition after using a drug he had synthesized in his own laboratory. The student had been examined by several doctors about six years earlier, including a group at the National Institute of Mental Health, and one doctor, Glenn Davis, had stuck with the case through the whole sequence. Ultimately, the patient died of a drug overdose, and during an autopsy it was found that the cells of the *substantia negra* portion of his brain were severely depleted.

Recent correlations between high cholesterol levels and heart disease have heightened the interest in factors controlling cholesterol levels in the body. The location of cholesterol receptor sites was unknown, but it was known that a genetic disease called familial hypercholesterolemia had a receptor defect that blocked the removal of lipoproteins from the blood. Human tissues could not be analyzed to determine which ones normally use low-density lipoprotein receptors to obtain cholesterol.

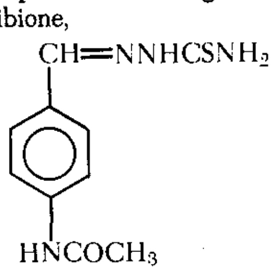
According to Gina Kolata (*8*), the break came when a Japanese veterinarian noticed that a male rabbit in his colony had 10 times the normal concentration in its blood. By appropriate breeding, a strain of rabbits with high cholesterol was developed, and these rabbits spontaneously developed coronary artery disease. These rabbits had a genetic defect, and their tissues take up low-density lipoproteins. The primary sites are the liver and the adrenal glands. Subsequent studies directed toward the role of tissue receptor sites in humans have increased our understanding of the whole cholesterol problem.

Cyclosporin A helps to prevent organ transplant rejection and has few side effects. The percentage of liver and kidney grafts surviving for one year has almost doubled since its introduction in 1979. The drug was originally isolated from two new strains of fungi found in the soil from two places: Wisconsin and Norway. What makes the story remarkable is that the finders were employees of Switzerland's Sandoz Corp., which has adopted the practice of asking its employees to pick up samples of soil when traveling abroad (*9*).

Two young boys who were burned in 1983, with scorched skin over 97% of their bodies, were among the first beneficiaries of a serendipitous discovery concerning skin grafts (*10*). While studying mouse tumors, Harvard's Howard Green found flourishing colonies of cells resembling those of the upper layer of living skin. These epithelial cells grew because of the presence of fibroblasts, a type of cell common to the connective tissue that makes up the dermis. Green saw that this had implications for burn patients because the cultured skin, derived from the victim, would not be rejected by the body's immune system. Cultured skin grown in this manner is loosened with a bacterial enzyme from the flask in which it was grown. Whole sheets of skin can be transferred to the body of the burn victim. Using minimal portions of the patient's own skin, we can create new skin of practically limitless area. The saga began, remember, with the study of mouse tumor cells.

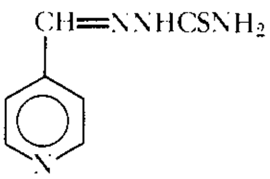
The antiepileptic properties of di-*n*-propylacetic acid DPA could hardly have been predicted, because convulsants often contain nitrogen or an aromatic moiety; DPA has neither. Among the roots of this story (*11*) is that, in 1963 Pierre Eymard prepared a series of derivatives of the vasodilator khellin to study their pharmacodynamic properties. Unfortunately, these compounds are water insoluble. His colleagues, H. Meunier and Y. Meunier, had used DPA as a relatively nontoxic solvent and suggested that Eymard try to use it for his compounds. The khellin derivatives did dissolve in DPA and showed pharmacodynamic properties. Shortly thereafter, H. Meunier used DPA as a solvent for a coumarin derivative, and the resulting solution protected rabbits against pentylenetetrazol-induced seizure. Suspicions were aroused, because no one had expected the coumarin compound to be active. Interest then centered on DPA itself, which was tested and found to be an anticonvulsant. The first clinical tests were conducted in 1964, and today DPA's use is widespread. Recall that DPA was originally the "inert" solvent.

In pharmaceutical research one usually screens all synthetic intermediates. That was the genesis of a valuable finding by researchers at E. R. Squibb and Sons (*12*), where a team of 24 researchers had tested more than 8000 compounds in the search for an antitubercular drug. As part of the study, Squibb developed a procedure for in vivo testing of the compounds. The drug used to evaluate this procedure was tibione,

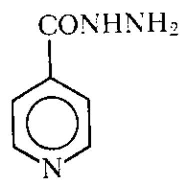



**Tibione**

which at the time was the most active of the synthetic tuberculostats but had serious side effects. In 1951, Harry L. Yale, at Squibb, decided that a compound having the structure




might have the antituberculous effect of tibione without its side effects. An intermediate in the synthesis was to be




which was known as isoniazid. When tested, isoniazid was far more effective against tuberculosis than any other known substance. It had minimal side effects. A variety of synthesis routes had been suggested for preparing the initially targeted compound, but isoniazid was an intermediate in the only route that was followed.

Paul Scheuer, at the University of Hawaii in Manoa, is an ardent believer in serendipity and mentions it in his writings. He was interested in the defensive secretions of *Phyllidia varicosa*, a brightly colored creature capable of delivering a sharp sting (*13*). The problem in identifying the active substance was that the organism seemed to stop producing mucus (the source of the compound) when it was in captivity. Why? No one knew, but one day an assistant, Jay Burreson, was scuba diving and noticed that *Phyllidia* was feeding off a white sponge. Analysis of the sponge showed that, indeed, it contained the active substance that had previously been ascribed to *Phyllidia*.

One of the most exciting developments in marine biology took place in 1968 as the result of the accidental sinking of the mini-submarine *Alvin* (*14*). It slipped away from its mother ship and sank in 1500 meters of water, fortunately with no one on board. Nine months later it was brought to the surface, and an inspection of the interior showed that lunches placed aboard the submarine by the crew in anticipation of the dive were in excellent shape. Apples retained their bright red color, soup remaining in a crushed Thermos had a natural taste, and a ham sandwich looked remarkably fresh. This prompted an immense interest in the microbiology of the deep sea and had two direct consequences. The first was that the ocean was no longer considered an apt spot for garbage disposal because the growth rates of microorganisms at the ocean floor were too slow to degrade large amounts of refuse. The second consequence was the discovery that there was a convenient way to study life at the ocean bottom that was far different from normal practices. Holger Jannasch and his colleagues at the Woods Hole Oceanographic Institution had been trying to retrieve samples of deep ocean water without affecting either the pressure or the temperature. This was extremely difficult, but the *Alvin* incident suggested that one could lower to the ocean floor syringes containing cultures of interest and then retrieve them after an established time. Comparisons could be made then with corresponding cultures that had been maintained at atmospheric pressure and at a temperature equivalent to that found at the ocean floor. The moral is, "If you can't beat 'em, join 'em." In reminiscing about the sinking of the *Alvin*, Jannasch noted that practically every important discovery made at Woods Hole resulted from some chance event.

What can we learn from these disparate examples? A critical component in all cases is the discerning eye of the careful and trained experimenter, who retains an open mind while setting out on a logical course of study. Researchers often complain of the restrictions placed on their research by granting agencies that insist that a proposed set of studies be followed rigorously. Fortunately, not all contract administrators are so short-sighted. Anthony Matuszko of the Air Force Office of Scientific Research is leery of any proposal in which goals beyond one year are predicted. Years of experience have shown the folly of such procedure. A disdain for what may be perceived as current practices was evident in the words of J. H. Humphrey (*15*): "As a member of various grant committees, I have come to realize that the manner in which grant applications must be formulated leaves little scope for discovering something new."

A similar note of caution was expressed by Sir Gustav Nossel (*16*): "In most discoveries as they first emerge, there is a sufficient element of doubt and tentativeness to give scope to a stern critic; it is relatively easy for an intelligent man to pick holes in the incomplete but truly new discovery. The overly critical, highly intelligent but unoriginal scientist can become a negative force in research."

Next we'll look at the role of serendipity in the physical sciences.

**References**

(1) Hannan, P. J.; Roy, R.; Christman, J. F. CHEMTECH, January 1988, pp. 18–21.
(2) Kauffman, G. B. *Educ. Chem.* **1980**, *17*, 180.
(3) Rossman, R. E. *Trans. Studies Coll. of Physicians of Phila.* **1966**, *33*, 104.
(4) Serafetinides, E. A. *Lancet* **1964**, *1*, 249.
(5) Hoffman, A. *LSD, My Problem Child*; J. P. Tarcher: Los Angeles.
(6) Kauffman, G. B. *Educ. Chem.* **1984**, *21*, 42.
(7) Lewin, R. *Science* **1984**, *224*, 1083.
(8) Kolata, G. *Science* **1984**, *221*, 1164.
(9) Kolata, G. *Science* **1983**, *221*, 40.
(10) Toufexis, A. *Time*, Aug. 27, 1984, p. 36.
(11) Kauffman, G. B. *Educ. Chem.* **1982**, *19*, 168.
(12) Kauffman, G. B. *J. Chem. Ed.* **1978**, *55*, 448.
(13) Scheuer, P. J. *Naturwissenschaften* **1982**, *69*, 528.
(14) Jannasch, H. W.; Eimhjellen, K.; Wirsen, C. O.; Farmanfarmaian, A. *Science*, **1971**, *171*, 672.
(15) Humphrey, J. H. *Annu. Rev. Immunol.* **1984**, *2*, 1.
(16) Nossal, G. Quoted in Beveridge, W. B. *Seeds of Discovery—Sequel to the Art of Scientific Investigation*; Norton: New York, 1981.

**Patrick J. Hannan,** now retired (5019 Sentinel Dr., Bethesda, Md. 20816; 301-320-5703), was a consultant in the Center for Survivability and Safety at the Naval Research Laboratory (NRL) in Washington. He received a B.S. in chemistry from Catholic University in 1942 and an M.S. in organic chemistry from the same institution in 1948. During his 31 years at NRL, he studied the reproducibility of assays using algae and yeasts. He pioneered the use of gas-exchange techniques for detecting transitory changes in the growth rates of microorganisms.

**Rustum Roy** is Evan Pugh Professor of the Solid State and Professor of Geochemistry at Penn State. He specializes in the design, synthesis, and preparation of new materials. His major research contributions include the invention of the sol–gel route to making ceramics, the synthesis of new and ultralow expansion ceramics, and radioactive waste solidification. He is a member of the National Academy of Engineering, the Royal Swedish Academy of Engineering Sciences, and the Indian National Science Academy. He has written widely on ethics.

**John F. Christman** was born in Terre Haute, Ind.; he received a B.S. (Chemistry) from the University of Notre Dame, a M.A. from Indiana University, and a Ph.D. from the University of Tennessee (Knoxville). He held a teaching position (to rank of Professor) at Louisiana State University (1950–66) and both teaching and administrative positions of Loyola University, New Orleans (1966–86). He is now retired but is actively engaged in writing and producing educational software, especially drills for standardized test preparation.

# Prince Serendip at work

Patrick J. Hannan
Rustum Roy
John F. Christman

"Most scientific discoveries are made by carefully thought out experiments and by logical conclusions based on proven theories." This myth has been perpetuated by teachers and scientists for the benefit of students and the public. Science is taught in a revisionist fashion. Discarded theories and failed experiments are not part of the curriculum—the excuse is lack of time. Reports of lucky accidents rarely appear in research journals and even less often in textbooks—the reason is lack of space. Thus neophytes and lay people see scientific progress as a straight line pushed along by abstract logic and objective experimentation. This view of science by the public has serious implications, especially when scientific evidence becomes the basis for societal decisions.

Serendipity—the ability to make desirable discoveries by accident—has often been the prime factor in technical progress. Pasteur knew that it takes a prepared mind to see the potential in an accident. Once that potential has been recognized, it takes skill to exploit the accident and transform it into a useful product. Here we'll illustrate how chance has often contributed to scientific and technological progress.

The story of the vulcanization of rubber is a good place to start. As far back as the 1830s, rubber was known to have two properties: It was sticky when it was hot and rigid when it was cold. Charles Goodyear was experimenting with a mixture of rubber and sulfur when some of the mixture fell on a hot stove. Those portions that were not badly scorched had become dry, flexible rubber that didn't lose its flexibility in the cold or its dryness in the warmth. When Goodyear experimented with higher temperatures than anyone else had tried, he ended up with vulcanized rubber (*1*).

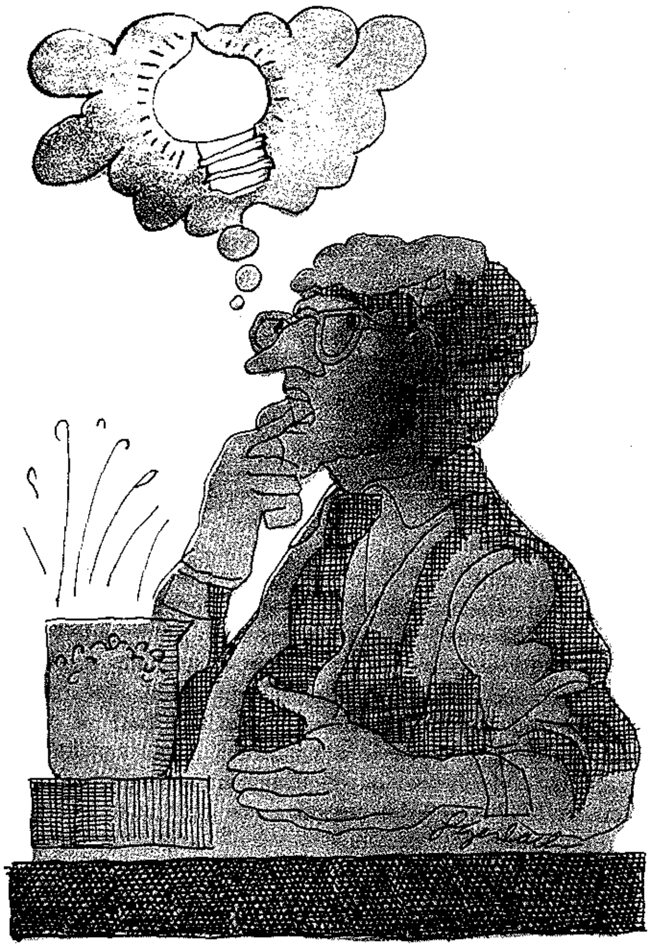
Teflon didn't start as a coating for frying pans. Du Pont was interested in finding and marketing a refrigerant gas to replace the $SO_2$ and $NH_3$ [illegible] early models of refrigerators. Roy [illegible] assigned the problem of preparing [illegible] first step was to synthesize about [illegible] tetrafluoroethylene (TFE), $CF_2{=}CF_2$, [illegible] small pressure cylinders. The second [illegible] weighing a cylinder of TFE and metering a stream of the gas over hot charcoal along with various ratios of HCl gas. On April 6, 1938, when one of the TFE cylinders was opened, no gas issued forth. The weight of the cylinder was unchanged from the day before, which indicated that the compound should still be inside. Fortunately, Plunkett and his assistant, Jack Reebok, decided to remove the valve of the cylinder and inspect the contents; what they found was a white, oily powder that turned out to have remarkable non-wetting properties and became known as Teflon.

Equally amazing, however, was an earlier development that was the prelude to this event. The compound $CCl_2F_2$ had been synthesized as a potential refrigerant by reacting $CCl_4$ with HCl in the presence of $SbF_3$ as a catalyst; there were only five 1-oz. bottles of $SbF_3$ in the whole country, and Du Pont had all of them. The product made with the first bottle of $SbF_3$ appeared to be the desired $CCl_2F_2$. Because all fluorine compounds were suspected of toxicity, the gas was mixed with air and tested on several guinea pigs. It was not toxic. But when the reaction was repeated

[illegible] MTECH, **1988**, *18*, pp. 18-21.

with the four remaining bottles of $SbF_3$, the product killed the guinea pigs. Subsequent investigations showed that their death was caused by phosgene, which resulted from a trace of moisture in the $SbF_3$. If any one of these four bottles of $SbF_3$ had been used first, the conclusion might have been drawn that $CCl_2F_2$ was toxic because of its fluorine content, and all interest in these compounds as refrigerants would have disappeared. Instead, both the refrigerant gas and Teflon became major products.

Just as Teflon resulted from a peculiar event involving a gas cylinder, so did the discovery of POLYOX water-soluble resins at Union Carbide. In 1951, George Fowler and Walt Dennison (3) opened a cylinder of ethylene oxide and were surprised that a black, viscous liquid came out. An investigation showed that, upon filtration, a black solid remained on the filter and the filtrate was colorless. Evaporation of this liquid resulted in a white solid that was water soluble; even dilute solutions made from it had a noticeable viscosity. Fowler and Dennison were able to duplicate the product formed in a "bad" cylinder of ethylene oxide by sealing the gas in a tube with $Fe_2O_3$ for five weeks at room temperature. With a variety of catalysts and reaction conditions, Union Carbide was able to make polymers having a wide range of molecular weights and physical properties. Today there is a family of resins ranging from 100,000 to 5,000,000 daltons. Packaging specialists have made sheets of film that can be fabricated into water-soluble packages containing measured quantities of materials. Agriculturalists imbed seeds at spaced intervals on such films, facilitating the planting of small seeds at specific spacings. The thickening properties of water solutions of these polymers have been used extensively in formulating cosmetics, lotions, shampoos, soap bars, and liquid dishwashing detergents. Because trace amounts of these polymers reduce friction of water flowing through pipe and hoses, fire departments can use smaller hoses to deliver a given volume of water or shoot the water greater distances. When Fowler and Dennison first noticed the black liquid in their cylinder of ethylene oxide, did they ever imagine the economic consequences of this chance event?



While we're on the subject of the polymerization of olefins, let's discuss for a moment the role of chance in finding new catalysts. Such polymerizations are often conducted with the aid of Ziegler–Natta-type catalysts, and, incidentally, the original Ziegler catalysts were discovered accidentally (4) because of the favorable results obtained with a dirty autoclave! Unlike Ziegler–Natta, there is a new type of catalyst that is extremely stable in solid form and soluble in various organic solvents. It was discovered accidentally by Walter Kaminsky and his associates (5) at the University of Hamburg. While they were studying bis (cyclopentadienyl) derivatives of titanium and zirconium complexed with aluminum alkyls and halides, they inadvertently allowed some water into the flask. This resulted in an unexpected increase in catalytic activity that was eventually attributed to aluminoxane. Following up on this fortuitous observation, they developed a highly active catalyst by adding aluminoxane to an aromatic solution of the commercially available dichloro- or dimethyl-derivatives of bis (cyclopentadienyl) zirconium. This catalyst has particularly good storage characteristics.

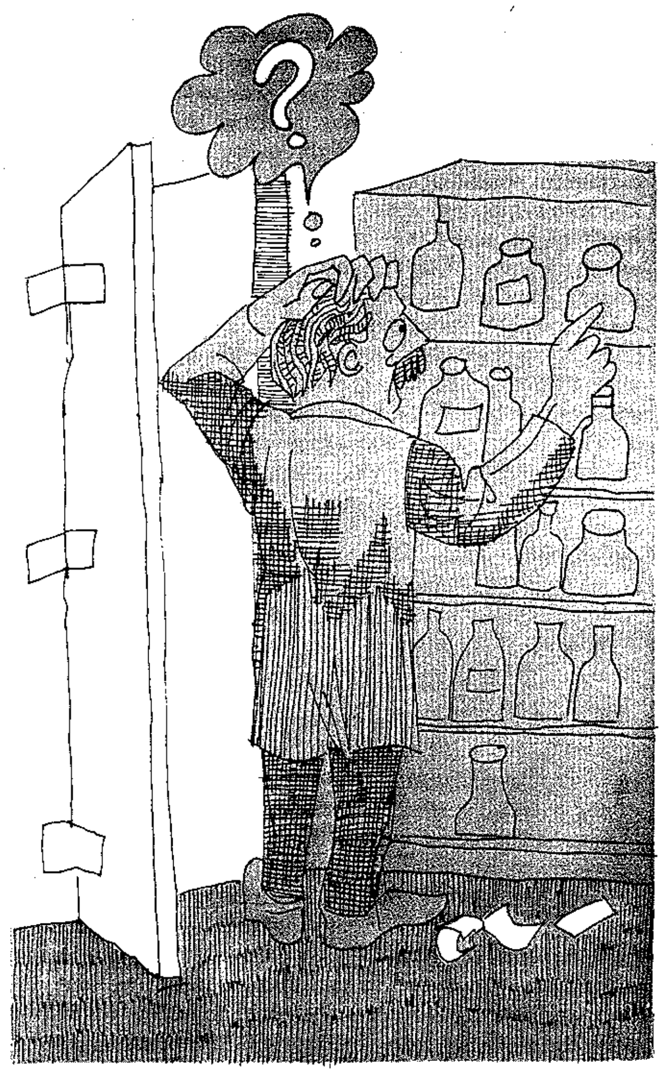
The synthetic sweetener industry has generated some problems but also large profits, and serendipity has played a large role throughout. If a chemist were to design a substitute for sucrose, he would hardly imagine that either aspartame or saccharin would fill the bill, because they bear no resemblence chemically to a carbohydrate. James Schlatter was trying to develop a test for an ulcer drug (*7*) when he refluxed some amino acids and accidentally ingested some of the product—and found it to be sweet. In the case of saccharin, Constantine Fahlberg was studying the oxidation of toluene sulfamide when some of the refluxing material boiled over and fell on his hand. He, too, tasted the product accidentally. One year, aspartame provided the G. D. Searle Co. with 70% of its total profits, and that surely is a sweet story.

Silicon carbide fibers now marketed under the name Nicalon are used to reinforce and toughen ceramics. They can be prepared in good yield from a solid polymer formed during the condensation of $Me_2SiCl_2$ in the presence of alkali metals. Here's how they were discovered: When Larry David (*6*) was a graduate student at the University of Wisconsin, he intended to produce a long polysilane chain analogous to carbon polymers. He did indeed obtain such a product, but he also got a byproduct that was considered laboratory "garbage." In time, the "garbage" proved to be a gem when it was shown that it could be thermally rearranged to render it meltable and soluble, after which it could be processed into silicon carbide fibers and films. In addition, a laboratory accident has led to a class of polymers that have potential use as silicon-based photoresists. A preliminary observation that the polymers could be doped to a conducting state (as high as 0.2 $\Omega^{-1}$ $cm^{-1}$ by $AsF_5$) indicated that electronic holes created by the electron-accepting dopant could move freely up and down the polysilane chains. The extent of this electron delocalization in the polymers was discovered when another scientist tried to measure the molecular weight of these polymers. David's research indicated that the polymers were at least 1000 silicon atoms long, but his colleague was finding only much lower molecular weights. Upon observing his colleague's technique, David found the reason for the large discrepancy: David's polymer had been dissolved in THF in a glass vial that had then been placed on a window ledge, where it was rapidly photolyzed. What was shocking was the size of the red shift of this absorbance—from the 270-nm region all the way to 330 nm in the near-UV—by lengthening the silicon chain to more than 1000 atoms.

Leo Baekeland was attempting to make shellac by reacting phenol with formaldehyde, but the product turned out to be Bakelite, which was one of the important early plastics and displaced shellac in many applications.

The refrigerated centrifuge (*13*) was developed because Michael Heidelberger had an assistant whose responsibility was to make crystalline equine oxyhemoglobin. The preparation had to be kept cold, so the centrifuge was kept in a refrigerated room. The assistant continually caught cold. That's why Heidelberger suggested to the International Centrifuge Co. that they build a centrifuge with a built-in cooling coil, which, of course, became a great seller. Heidelberger's reward? He received $50 for writing an instruction booklet for the instrument.

Mention of the refrigerated centrifuge brings to mind an accidental discovery concerning the science of preserving cells, tissues, and organs at low temperature. As



told by P. N. Campbell (*14*), in 1949 he moved to the National Institute for Medical Research at Holly Hill, Hampstead, a suburb in north London. That laboratory shared a cold room with a small team stationed at Mill Hill, several miles away, that was studying methods for the preservation of fowl sperm at low temperatures. Because fructose is normally present in the seminal fluid of many animals, the Mill Hill group conducted numerous experiments with varying concentrations of fructose, but without success. It was not uncommon in those days for paper labels to fall off bottles in a cold room (Magic Marker pens were still unknown), and that is how Campbell's group came to use the contents of an unlabeled bottle in one of their experiments. The results exceeded anything they had done previously. The contents of the unlabeled bottle turned out to be a solution of glycerine placed in the store room by the occupants of the other laboratory.

The Freeport McMoRan Co. had been enjoying success with its production and sale of ammonium phosphate as a fertilizer, not realizing that it had been neglecting an important byproduct. One of its bench chemists happened to read in *Chemical & Engineering News* that there were substantial amounts of trace metals in the phosphate beds that they were using, including 0.013% uranium, which could amount to a staggering figure if recovery could be made reasonably. Attempts to extract the uranium were unsuccessful for a number of reasons, one being that the feed was so low in uranium. Eventually two serendipitous findings made the process feasible. The first was the discovery of the synergistic extractant combination of di-2-ethylhexylphosphoric acid and trioctylphosphine oxide; this wasn't without problems, however, because lots of ammonia was used in the process, which caused iron hydroxide to precipitate. The investigation of this problem led, however, to a second breakthrough—reductive stripping. The researchers had thought that by contacting the uranium-loaded extractant with a strong complexing ion, fluoride, they could strip small amounts of U(VI) from the extractant and by a series of electrolytic reductions recover $UF_4$ as a product. Recovering efficiencies were not high, but eventually they contrived a way to substitute elemental iron for the electrolytic cell and came up with a two-cycle process that solved the problems associated with the earlier processes. Since the initial operation of this program in 1978, the company has had gross sales of more than $350 million in uranium (*9*).

An interesting development at the Xerox Corp. was described by Dorsey (*10*), writing in the *Rochester Democrat and Chronicle:* "Robert Grundlach, Xerox's top inventor, made one of his best discoveries in a hotel room. While on a trip, he was polishing his shoes with a cloth provided by his hotel. It occurred to him he could use a similar cloth inside a copier to clean away excess toner (the black granules used to create a xerographic image). The discovery made possible the elimination of a large, complicated vacuum system, thus opening the way for compact desk-top copiers. That chance encounter with a polishing cloth, far from the rigors of the laboratory, meant a whole new market for the Xerox Corp."

The product known as Avicel is the most hydrophilic polymer known and is sold in bulk for use in low-calorie foods and for food stabilization. According to Jean Bernius (*11*), Avitene (the antecedent compound from which Avicel is made) is an entirely new form of natural collagen, and in its gel form it is a water dispersion of collagen microcrystals. The discovery of this compound came about when Orlando A. Battista had been working with rayon to make a better tire. An assistant had whirled some rayon and acid in a blender, producing a fluffy white mess that was a disgusting result in the eyes of the assistant but was cause for celebration on the part of Battista, who sensed the value in the finding. At the time of Bernius's article, more than 120 million pounds of Avicel had been sold to the food industry, making possible the preparation of cream sauces and salad dressings that can be sterilized in their containers without separation or running.

The use of lithium for the treatment of mental illness is the basis for a large industry that stemmed from an observation by John Cade (*12*). Several anions had been considered as potential drugs for use against schizophrenia. Cade's insight into the study was that it was lithium, the cation associated with some of the anions, that seemed so promising. Subsequent experimentation proved that Cade was correct.

Such is the nature of many discoveries that might result from illogical events. Admittedly, some of the examples we have presented are trivial, although interesting, but some of our examples have had monumental economic consequences. In all cases there was a willingness to explore the unknown for practically no reason other than scientific curiosity, which makes the results particularly attractive. Alfred North Whitehead was probably right on the money when he said that "all truly great ideas seem somewhat absurd when first proposed."

In our next article, we'll show how luck has shaped the modern practice of medicine.

## References


(1) Asimov, I. *Biographical Encyclopedia of Science and Technology*; Doubleday: Garden City, N.Y., 1972.
(2) Plunkett, R. Presented at the AAAS Symposium on the Role of Chance and Serendipity in Science, Philadelphia, May 28, 1986.
(3) Myerly, R. C. *J. Chem. Ed.* **1980**, *57*, 437.
(4) Davies, D. S. *Chem. Eng. News* March 6, 1978, p. 22.
(5) *Chem. Eng. News* July 4, 1983, p. 29.
(6) David, L. D. Presented at the AAAS Symposium on the Role of Chance and Serendipity in Science, Philadelphia, May 28, 1986.
(7) *Wall Street Journal* Sept. 14, 1984, p. 3.
(8) Kauffman, G. B.; Priebe, P. M. *Ambix* **1978**, *25*(III), 197.
(9) Miller, D. J. Presented at the AAAS Symposium on the Role of Chance and Serendipity in Science, Philadelphia, May 28, 1986.
(10) Dorsey, D. *Democrat and Chronicle* (Rochester, N.Y.) May 11, 1986.
(11) Bernius, J. *J. Chem. Ed.* **1975**, *52*, 155.
(12) Cade, J. F. J. *Med. J. Aust.* **1949**, *36*, 349.
(13) Heidelberger, M. *Annu. Rev. Microbiol.* **1977**, *31*, 1.
(14) Beveridge, W. *The Art of Scientific Investigations*; Norton: New York, 1957.



**Patrick J. Hannan**, now retired (5019 Sentinel Dr., Bethesda, Md. 20816; 301-320-5703), was a consultant in the Center for Survivability and Safety at the Naval Research Laboratory (NRL) in Washington. He received a B.S. in chemistry from Catholic University in 1942 and an M.S. in organic chemistry from the same institution in 1948. During his 31 years at NRL, he studied the reproducibility of assays using algae and yeasts. He pioneered the use of gas-exchange techniques for detecting transitory changes in the growth rates of microorganisms.



**Rustum Roy** is Evan Pugh Professor of the Solid State and Professor of Geochemistry at Penn State. He specializes in the design, synthesis, and preparation of new materials. His major research contributions include the invention of the sol-gel route to making ceramics, the synthesis of new and ultralow expansion ceramics, and radioactive waste solidification. He is a member of the National Academy of Engineering, the Royal Swedish Academy of Engineering Sciences, and the Indian National Science Academy. He has written widely on ethics.



**John F. Christman** was born in Terre Haute, Ind.; he received a B.S. (Chemistry) from the University of Notre Dame, a M.A. from Indiana University, and a Ph.D. from the University of Tennessee (Knoxville). He held a teaching position (to rank of Professor) at Louisiana State University (1950–66) and both teaching and administrative positions of Loyola University, New Orleans (1966–86). He is now retired but is actively engaged in writing and producing educational software, especially drills for standardized test preparation.